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CC: Jones, Lindsey [jones.lindsey@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]
Subject: perchlorate
Attachments: Clewell etal (2019) ClO4 BBDR Review RegToxPharm.pdf

This came my way today. Haven't read yet, but thought you may be interested.

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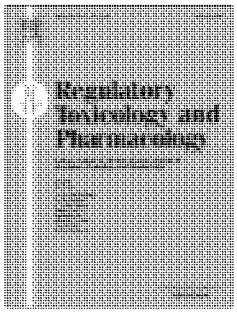

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An Evaluation of the USEPA Proposed Approaches for Applying a Biologically Based Dose-Response Model in a Risk Assessment for Perchlorate in Drinking Water

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ABSTRACT

The United States Environmental Protection Agency's (USEPA) 2017 report, "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water", proposes novel approaches for deriving a Maximum Contaminant Level Goal (MCLG) for perchlorate using a biologically-based dose-response (BBDR) model. The USEPA (2017) BBDR model extends previously peer-reviewed perchlorate models to describe the relationship between perchlorate exposure and thyroid hormone levels during early pregnancy. Our evaluation focuses on two key elements of the USEPA (2017) report: the plausibility of BBDR model revisions to describe control of thyroid hormone production in early pregnancy and the basis for linking BBDR model results to neurodevelopmental outcomes.. While the USEPA (2017) BBDR model represents a valuable research tool, the lack of supporting data for many of the model assumptions and parameters calls into question the fitness of the extended BBDR model to support quantitative analyses for regulatory decisions on perchlorate in drinking water. Until more data can be developed to address uncertainties in the current BBDR model, USEPA should continue to rely on the RfD recommended by the NAS (USEPA 2005) when considering further regulatory action.

Keywords: perchlorate, risk assessment, MCLG, BBDR model

INTRODUCTION

From a regulatory perspective, the critical effect of concern from exposure to perchlorate is disruption of thyroid function and the potential for thyroid-hormone-related effects on neurodevelopment in gestation; these effects represent downstream events resulting from competitive inhibition of iodide uptake by the perchlorate ion (USEPA 2002). Based on an analysis of the mode of action for perchlorate, the United States Environmental Protection Agency (USEPA) (2002) determined that inhibition of thyroid iodide uptake could be used as an obligatory precursor for these critical effects in a harmonized cancer/noncancer risk assessment for perchlorate (Figure 1). This mode-of-action directed risk assessment approach was used in the derivation of the current Reference Dose (RfD) for perchlorate of 0.0007 mg/kg/day (USEPA 2005). Following the recommendations of the National Academy of Sciences National Research Council (NRC) (2005), the point of departure (POD) for this RfD was a reported No Observed Effect Level (NOEL): a non-statistically significant mean of 1.8% (standard error of the mean 8.3%) decline in radioactive iodine uptake (RAIU) in healthy adults following two weeks exposure to a daily perchlorate dose of 0.007 mg/kg/day (Greer et al. 2002). An intraspecies uncertainty factor of 10 was applied to protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency.

Subsequently, the USEPA Office of Drinking Water (2008) published an Interim Health Advisory Level for perchlorate of 15 µg/L, based on the USEPA (2005) RfD of 0.7 µg/kg/day, as recommended by the NRC (2005). Determination of this Interim Health Advisory Level considered Physiologically-Based Pharmacokinetic (PBPK) Modeling (Clewell et al. 2007) to estimate the potential effect of perchlorate on iodide uptake in several sensitive subgroups, including the pregnant woman and fetus, the lactating woman and neonate, and the young child. Despite widespread scientific acceptance of iodide inhibition as an obligatory precursor to downstream toxicity endpoints, there was remaining concern regarding the level of protection for the population perceived to have the greatest susceptibility – the fetuses of hypothyroid mothers.

Over the next several years, the focus of research on perchlorate shifted to the development of a biologically based dose-response (BBDR) model of the hypothalamic-pituitary-thyroid (HPT) axis that could be linked with the PBPK model of perchlorate and iodide to predict dose-dependent interactions

of perchlorate with iodine hormone homeostasis as a function of iodide intake in an effort to more quantitatively account for the effects of low dietary iodide intake and hypothyroidism in pregnant women on fetal development (McLanahan et al. 2008, 2009; Fisher et al. 2012; Lumen and George 2017a, 2017b; Lumen et al. 2013, 2015).

The USEPA Science Advisory Board (SAB) (2013) report on perchlorate in drinking water supported the utility of BBDR modeling to help characterize the potential for neurological effects from perchlorate exposure:

> "As perchlorate research continues, studies in animals may provide important insights into the neurobehavioral consequences of perchlorate exposure. A physiologically-based pharmacokinetic/pharmacodynamic framework is well suited to help place these findings in the context of human perchlorate exposure."

The USEPA SAB (2013) identified a number of areas for improvement or modification of the existing models. However, they also noted that "Models can always be improved, but the goal is to have a model that is fit for the intended purpose.", apparently cautioning against perpetual model refinement at the expense of implementation, echoing the concern of the renowned statistician, George E.P. Box, who famously used to say: "All models are wrong but some are useful" (Box 1976).

Recently, the USEPA's Office of Ground Water and Drinking Water (USEPA 2017) responded to the Science Advisory Board recommendations and proposed novel approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate, including the use of BBDR modeling in their report entitled "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water". This MCLG approach (USEPA 2017) includes revisions to a previously developed and peer reviewed BBDR model (McLanahan et al. 2008, 2009; Fisher et al. 2012; Lumen and George 2017a, 2017b; Lumen et al. 2013, 2015) that was extended to predict the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages. These revisions aim to address suggestions by the USEPA SAB (2013), including the following:

- Derivation of a perchlorate MCLG that addresses sensitive life stages through PBPK/PD modeling;

- Expansion of the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- Utilization of a mode of action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition to thyroid hormone changes and finally neurodevelopmental impacts; and
- Extension of "the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (USEPA SAB 2013, p. 19).

Model revisions presented in the USEPA (2017) report include: incorporating a description of the physiology of early pregnancy, biological feedback control of hormone production via thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (hCG), and a description of the response to lower levels of iodide nutrition. In addition, an attempt was made to calibrate the model's behavior for upper and lower percentiles of the population, in addition to the population median, for thyroid hormone production. The report also included an uncertainty analysis for key BBDR model parameters.

For the development of the MCLG, USEPA (2017) proposed a two-stage approach linking the revised BBDR model results ("Stage 1") with quantitative information on neurodevelopmental outcomes from epidemiological studies ("Stage 2"). Stage 1 describes the thyroidal hormone levels in women of childbearing age with low to adequate iodide intake. In this stage, the revised BBDR model is applied to predict the relationship between perchlorate exposure and changes in thyroid hormone levels in early pregnancy. Data for Stage 2 of the approach is provided from epidemiological studies evaluating maternal thyroid hormone levels in early pregnancy and the relationship between changes in these levels and the observation of neurodevelopmental outcomes. The USEPA (2017) report also described development of a novel population-based approach that uses the revised BBDR model to estimate changes in levels of selected thyroid hormones, specifically free tetraiodothyronine (fT4) and TSH, resulting from perchlorate exposure that may result in an increase in the prevalence of hypothyroxinemia in pregnant women. Hypothyroxinemia (low circulating concentrations of fT4) is

111 often associated with hypothyroidism (low concentrations of fT4 despite increased concentrations of
112 TSH).

113 The evaluation and (potential) application of the perchlorate BBDR model will serve as an important
114 precedent for future consideration of such models by the agency, as it is only the second such model
115 to be seriously evaluated by USEPA and subjected to external peer-review. The first BBDR model to
116 be considered, formaldehyde nasal carcinogenicity developed by Conolly and colleagues (2003, 2004),
117 has been under consideration by the agency for more than a decade. Interest in the use of BBDR
118 modeling in risk assessment peaked in the 1990s when the draft USEPA (2003) Cancer Guidelines
119 identified these models as the preferred option for performing a cancer dose-response. However,
120 since that time, work in this area has waned, possibly due to the perceived difficulty of gaining
121 regulatory acceptance. By their nature, BBDR models are descriptions of complex biological systems
122 that necessarily include significant uncertainty. The challenge going forward will be to develop
123 approaches for characterizing that uncertainty in a risk assessment context and ensuring that these
124 complex models are fit for their intended purpose. It is with this consideration in mind that we have
125 performed a focused evaluation of the proposed USEPA (2017) approaches.

126 Our critical review focused on two key areas of importance for determining whether the current BBDR
127 model is fit for the purpose of supporting regulatory decisions based on predicted effect of perchlorate
128 exposure on human fetal development:

129 1. Evaluation of USEPA (2017) model revisions to the peer reviewed BBDR models, including
130 extending the model to early pregnancy, incorporating biological feedback control of hormone
131 production via thyroid stimulating hormone (TSH) and human chorionic gonadotropin (hCG)
132 signaling, calibration of the model for thyroid hormone effects, and uncertainty analysis for
133 key parameters. This evaluation included comparison of model output to results from key
134 human studies identified in previous assessments (Greer et al. 2002, Braverman et al. 2006,
135 Téllez et al. (2005a, 2005b), as well as in the USEPA (2017) document (Steinmaus et al.
136 2016);
137 2. Evaluation of USEPA (2017) approaches for linking BBDR results to neurodevelopmental
138 outcomes and identification of published literature to develop the quantitative relationship
139 between thyroid hormone levels and neurodevelopmental outcomes; and

After describing the results of this evaluation, we present a comparison of the results from the USEPA (2017) approach with results from previous USEPA assessments, in order to put the uncertainties in the BBDR approach in perspective against the potential impact of the new approach on the existing regulatory guidelines for perchlorate USEPA (2005, 2008).

METHODS

Evaluating Stage 1 of USEPA MCLG approach: Stage 1 of USEPA's MCLG approach relies upon the application of the BBDR model to predict the effect of perchlorate on the thyroid hormone in pregnant women at different iodine nutrition levels, with the goal of predicting fT4 hormone reduction in pregnant women with low dietary iodide. To evaluate the utility of the proposed model to support such predictions, we independently ran the model and tested model predictions against data from multiple studies. These exercises attempted to both duplicate BBDR model results for datasets that were used by USEPA (2017) to calibrate the model and to test the ability of the BBDR model to predict the well-described precursor event inhibition of iodide uptake, which was successfully described with previous versions of the perchlorate PBPK models (Merrill et al. 2003; Clewell et al. 2007). These simulations included:

- Steinmaus et al. 2016 – cross-sectional epidemiological study evaluation of serum and urine in pregnant women in California: used in USEPA (2017) to evaluate BBDR model predictions of perchlorate effects on fT4 and TSH
- Greer et al. 2002 – 14-day controlled perchlorate dose study in male and female adults in the US: used in USEPA (2017) to estimate urinary clearance parameters in BBDR model
- Braverman et al. 2006 – 6-month controlled perchlorate dose study in male and female adults: not used in USEPA (2017)
- Téllez Téllez et al. 2005a, 2005b – longitudinal epidemiological study in pregnant and lactating women in Chile: used in USEPA (2017) to estimate urinary clearance parameters in BBDR model

In our efforts to produce these simulations, it was noted that instructions provided in the USEPA documentation for running the model for different scenarios, and documentation of the rationale for the model parameter values associated with them, are often inadequate and lack transparency; this deficiency is exacerbated by the number of permutations of parameter settings used in the scripts that

generate the results in the document. The complexity of the BBDR model makes it difficult to perform this evaluation, even though it has been conducted by experienced modelers.

Evaluating Stage 2 of USEPA MCLG approach: Stage 2 of USEPA's approach involved evaluating the published epidemiological literature to identify publications that would define quantitative relationships between thyroid hormone levels and neurodevelopmental effects. The USEPA approach was focused on the identification of studies that provided information on levels of fT4 in pregnant mothers during early gestation and the potential for changes in neurodevelopmental outcomes in their offspring. Through targeted literature searching and recommendations from the Science Advisory Board (SAB), a total of 55 studies were identified by USEPA to provide information on altered maternal thyroid hormone levels and offspring development. These studies were divided into three groups to facilitate evaluation:

- Group 1 – studies that may be able to quantitatively describe a relationship between incremental alterations in maternal thyroid hormone levels and alternations in offspring development;
- Group 2 – studies that do not have data from which to derive a quantitative relationship between maternal hormones and offspring neurodevelopment, but instead present only a categorical analysis with thyroid hormones below and above a defined cut point and adverse neurodevelopmental outcomes; and
- Group 3 – studies that present an analysis that is not directly compatible with BBDR output.

Of the 55 studies, 15 were identified as Group 1, 14 were identified as Group 2, 26 were identified as Group 3. The 15 Group 1 studies were then evaluated further and only 5 were deemed useful by the USEPA for further quantitative analysis to attempt to connect alterations in thyroid hormone levels to alterations in neurodevelopment. in our evaluation, we performed a critical review of the USEPA Stage 2 approach and the study summaries provided in USEPA (2017), considering the most recent recommendations from the National Research Council (NRC 2014) on systematic review of the literature and evidence integration.

RESULTS

Evaluation of the Perchlorate BBDR Model for Early Pregnancy

The draft MCLG approach (USEPA 2017) is based on a hypothesized mode of action (Figure 1) for neurodevelopmental outcomes resulting from development of hypothyroxinemia from perchlorate-induced inhibition of iodide uptake in the thyroid. As noted in USEPA (2017):

> "Thyroid hormones are essential for the development and differentiation of the developing brain. The brain and spinal cord begin development in the first half of the first trimester. fT4 passes through the blood-brain barrier via multiple, specific transporter proteins. Next, T4 is converted to T3 by the developing glial cells and then transported to neurons. T3 then interacts with nuclear receptors to tightly regulate gene expression so that neurogenesis, synaptogenesis, neuronal migration, cell differentiation, and myelination are developmentally appropriate. Deficiencies in thyroid hormones through iodine deficiency, congenital hypothyroidism, or maternal hypothyroidism/hypothyroxinemia can result in neurological impairments and intellectual deficits (Morreale de Escobar, Obregón, & Escobar del Ray 2000)."

As recommended by the USEPA SAB (2013), the USEPA extended a published BBDR model for perchlorate induced hypothyroxinemia in late gestation (Lumen et al. 2013; Lumen and George 2017a, 2017b) to address the sensitive population of concern for exposure to perchlorate: the fetuses of hypothyroxinemic women during early pregnancy (Figure 2). These concerns were motivated by new studies (Steinmaus et al. 2016), suggesting an association between perchlorate exposure and decreased levels of free thyroxine (fT4) in pregnant women. Because the fetus is entirely dependent on maternal thyroid hormones for neurodevelopment in early gestation (Clewell et al. 2007; Howdeshell 2002), the endpoint of interest was defined as reduction in maternal fT4 in early pregnancy and the perchlorate BBDR models were extended to describe hormone homeostasis during gestation. Expansion of the original models of perchlorate and iodide (Clewell et al. 2007) to predict the impact of perchlorate exposure on fT4 during early pregnancy, however, is complicated by the significant variability in the levels of fT4 in the general population and the challenges in measuring fT4, as well as the dynamics of changing hormones through the course of gestation and the uncertainty in identifying the level of alteration that may lead to hypothyroidism and fetal effects.

224

225 According to the "American Thyroid Association Task force on Thyroid Disease During Pregnancy and
226 Postpartum", isolated hypothyroxinemia is defined as a normal maternal TSH concentration in
227 conjunction with fT4 concentrations in the lower 5th or 10th percentile of the reference range
228 (Stagnaro-Green et al. 2011). USEPA (2017) has also focused on selected percentiles of the reference
229 range; however, reference ranges can vary from population to population according to the *2017*
230 *Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease*
231 *During Pregnancy and Postpartum* (Alexander et al. 2017). Even within US populations and across
232 ethnic groups, the 2.5th percentile can vary by up to 2 pmol/L or approximately 20% (9.3-11.4
233 pmol/L as reported by Alexander et al. 2017).

234 The variation in fT4 reported in the published literature during early pregnancy is provided in USEPA
235 (2017), Appendix A, Figure A-33 and reproduced in Figure 3. The levels of fT4 during early
236 pregnancy, based on the studies identified by USEPA (2017), appear to range from approximately 13-
237 17 pmol/L. This range is consistent with the range of baseline fT4 means reported in the Greer et al.
238 (2002) study of approximately 1.1 – 1.3 ng/dL (14 - 17 pmol/L). However, the 50th percentile BBDR
239 model predictions at zero dose perchlorate and 170 µg/day iodine intake are approximately 10 pmol/L
240 at gestation weeks 12, 13, and 16, considerably below these reported values.

241

242 Measuring fT4 in the presence of high concentrations of bound T4 is challenging, especially in
243 conditions where binding proteins are altered such as during pregnancy (Alexander et al. 2017).
244 Measurement techniques are prone to inaccuracy during pregnancy due to disruption of the original
245 equilibrium. The 95% fT4 reference intervals decrease gradually with advancing gestational age: from
246 1.08– 1.82 ng/dL (approximately 13.9 – 23.5 pmol/L) in week 14 to 0.86–1.53 ng/dL (approximately
247 11.1 – 19.8 pmol/L) in week 20 (Alexander et al. 2017).

248 Extending the thyroid BBDR model to address early gestation is particularly challenging due to
249 the complex interaction between thyroid homeostasis and gestational development.
250 Considering the addition of TSH feedback dynamics, and an adjustment factor to match
251 specific population percentiles, there is reason for concern regarding the uncertainty of the

revised model predictions under low iodide intake conditions. Some of these concerns are highlighted below:

Description of hCG dynamics: Human chorionic gonadotropin (hCG) levels rise in early pregnancy and this in turn increases both sodium-iodide symporter (NIS) uptake activity and T4 production. hCG is structurally similar to TSH and, like TSH, increases thyroidal iodide uptake and thyroid hormone synthesis by binding to the thyroid-stimulating hormone receptor (TSHR) (Hoermann et al. 1994). In the model, hCG levels are calculated as a function of gestational age, using an equation for the parameter HCGREG (Figure 4, purple curve), and these changing levels are used to increase the rate of T3 and T4 production as a function of the hCG concentration:

HCGreg = 1 + 0.00354*hCG

The variation of hCG over the duration of gestation is based on direct measurements of hCG in pregnant women (Korevaar et al. 2015). However, the concurrent increase in thyroidal iodine uptake is described in the model based on an empirical relationship between gestational age in weeks (GW) and radioactive iodide uptake, using an equation for the parameter VCHNG (Figure 4, green curve):

$$VCHNG(GW) = 1 + 0.076 \cdot GW - 0.0025 \cdot GW^2$$

Thus the model does not correctly attribute the gestational control of NIS uptake to hCG, when in fact both uptake and hormone synthesis respond to the same changes in hCG (Pesce and Kopp 2014). By using different equations for the time-dependence of hCG-stimulated uptake and hormone production (Figure 4) the model decouples processes that are fundamentally linked by their biology. Figure 4 depicts the time-course of the parameters controlling changes in iodide uptake (VCHNG) and hCG hormone levels (HCGreg) over the course of gestation. While the biology indicates a proportional relationship between the two parameters, the equations used in the model are not parallel. Elucidating the impact of this decoupling is challenging, and is beyond the scope of this review, since it would have to be investigated at a large number of time-points throughout pregnancy and under different conditions of iodine intake, but the disparity between the model description and the underlying biology justifies caution regarding its predictions of T4 and TSH at different gestational ages, as these parameters govern hormone production and

release. We address the impact of the discrepancy between the time-courses for HCGREG and VCHNG in a later section.

Damping of TSH response: The USEPA (2017) BBDR model includes a parameter, pTSH (power to which the ratio of current TSH to the TSH set-point is raised), that reduces the response of the thyroid to increases in TSH:

$$TSHreg = (TSH/TSH_0)^{pTSH}$$

Using this equation, a pTSH exponent of 0 would represent no control of thyroid function by TSH and an exponent of 1 would represent a linear response of thyroid function to changes in TSH. In their calculations of the effect of perchlorate on the prevalence of hypothyroxinemic pregnant women, the USEPA (2017) use a pTSH exponent of 0.398, which results in a response to TSH that is substantially less than linear, an assumption that is inconsistent with the fundamental biological relationship between TSH and thyroid hormones (production and release of T3 and T4), effectively decoupling a relationship that has been well established in the medical, pharmacological and toxicological communities. USEPA (2017) describes the rationale for this parameter: "The NHANES data do not show a clear correlation between TSH and fT4, so within that data set they vary independently. One could assume, therefore, that individuals with an average fT4 and high TSH have that combination because their thyroid has a weak response to TSH, and vice-versa." To address this concern, USEPA (2017) estimated a lower and upper bound for pTSH as (median TSH)/(97.5th percentile TSH) = 0.398 and (median TSH)/(2.5th percentile TSH) = 3.09, respectively, with a median value of pTSH = 1. Thus, this parameter is used to attempt to represent disease states where the individual's thyroid is either exquisitely sensitive or insensitive to TSH stimulation. At lower values, this parameter reduces the impact of TSH on the Vmax for thyroid iodide uptake as well as the rate constants for T4 and T3 production in the thyroid. However, the USEPA (2017) also states that: "The coefficient, pTSH, is included…to allow for tuning of the strength of the TSH feedback, but in practice model simulations versus data appear quite adequate with pTSH=1." Concerns about this parameter are two-fold. First, the complexity of the model and various runtime scripts makes it nearly impossible to determine the use of this

parameter during some of the model assessment and risk assessment simulations presented in USEPA (2017). Second, using point estimate population level data to define the quantitative temporal relationship between two fundamentally linked processes at the individual level is scientifically inappropriate. To understand the biological feedback within a single individual (i.e. to determine the relationship of TSH to T3/T4 and Vmax for a hypothyroid or hyperthyroid individual), matched samples would be needed for TSH, T3 and T4. This information – to our knowledge – is not available from NHANES. Thus, the epidemiological point estimate data are being used well beyond its domain of applicability to predict the quantitative outcome of disease states.

Calibration of hormone production rates: The model uses a baseline first-order constant calibrated to NHANES 2007-2012 median, 10th, or 90th percentile non-pregnant data (fT4, fT3, T4 and T3 concentrations). The model parameter for the rate of production of T4 (KProdT4F) for the median NHANES calibration used in USEPA (2017) is 6.25*10-7 /hr/$kg^{0.75}$ (their Table A-2), which is 4-fold lower than the value of 2.45 x 10-6 estimated for the published model (Lumen et al. 2013), which was based on the data of Nicoloff et al. (1972). However, the use of a T4 production rate that is lower than the published value is not adequately justified, given the importance of this parameter, which has a direct impact on predictions of fT4 changes, the intended application of the model. This baseline value is then scaled in pregnancy through GW 16 (peak occurring ~ GW 9) based upon placental hCG increase over this time, according to the linear relationship from Glinoer (1997): hCGreg = 1 + 0.00354 x hCG.

Affinity of NIS Iodine uptake: The model uses a Km for perchlorate binding to the NIS (KmNIS_P) that is 3-fold lower than the value estimated by Lumen et al. (2013) (i.e. a 3-fold higher affinity). Specifically, the new Km represents the 2.5th percentile lower confidence limit of the population median based upon the USEPA (2017) reanalysis of Greer et al. (2002). The median value (50th percentile = 0.73 µM) is similar to that obtained from a re-analysis of *in vitro* binding data, 0.59 µM (Schlosser 2016); the use of a value of KmNIS_P = 0.489 µM makes perchlorate 3 times more effective at competitive inhibition of NIS compared to the model of Lumen et al. (2013). This revision to the Km in USEPA (2017) necessitated revisions to the Vmax (VmaxNISF_thy_P) and urinary excretion parameters (CLFUP) (Table 1 of USEPA 2017), further affecting the model's

sensitivity to changes in perchlorate dose, particularly under conditions of low iodide. Thus, The USEPA (2017) BBDR model predicts much greater effects of perchlorate on iodide uptake than any previous version of the model, without justification for re-estimating these parameters rather than using the published values.

Assumptions regarding thyroidal iodide storage: Plots of NHANES 2007-2012 data for non-pregnant women demonstrated little relationship between iodine intake and fT4, even at iodide intake levels below 75 µg/day (Figure A-54 of USEPA 2017; reproduced in Figure 5a). USEPA (2017) used data on the relationship between thyroidal iodide stores (mg) and iodine intake from Delange (2000), which assumes depletion of fT4 at iodide intake levels below 100 µg/day. As is clear from Figure 5b, this assumed model behavior at concentrations below 100 µg/day, which drives model predictions at low intakes, is inconsistent with the NHANES data and could result in overprediction of fT4 responses at moderately low intakes of iodide, including the ranges simulated in the USEPA report. This possibility was investigated in this evaluation and the results are discussed in the next section.

Evaluation of BBDR Model Behavior

Comparison to the Steinmaus et al. 2016 Results

In Appendix B of USEPA (2017), a comparison of the predicted changes in both fT4 and TSH from the BBDR model were compared to the results reported by Steinmaus et al. (2016). The Steinmaus et al. (2016) study was conducted to evaluate the potential for perchlorate exposure to impact thyroid hormone levels in pregnant women (any trimester) in San Diego. They reported an effect of perchlorate on fT4 levels to be similar among women with both low iodine (<100 µg/day) and normal (100-300 µg/day), with a greater effect of perchlorate observed among pregnant women in the high iodine intake group (>300 µg/day). They further noted that this result is in contrast to some previous results from NHANES (Blount et al. 2006) and may be due to the overall iodine sufficiency in the studied population or the fairly long time between urine iodine and serum thyroid hormone sample collection (about 9 weeks).

The comparison of the predicted fT4 changes from the BBDR model and the Steinmaus et al. (2016) results associated with changes in perchlorate dose are reported in Figure B-1 of Appendix B of USEPA (2017) and reproduced in Figure 6. This comparison, which we were able to reproduce using the

366 USEPA (2017) BBDR model, clearly highlights the differences between the model predictions and the
367 published human data. The USEPA (2017) BBDR model simulations with normal iodine intake (170
368 µg/day) demonstrate no change in fT4, which is consistent with other studies in which no impact on
369 fT4 has been observed at doses up to 7 µg/kg/day perchlorate (Greer et al. 2002; Braverman et al.
370 2006). The USEPA (2017) BBDR model greatly under-predicts the changes in fT4, even in the
371 scenario with low dietary iodine intake (75 µg/day), in comparison to the changes reported by
372 Steinmaus et al. (2016). This discrepancy raises concerns about the ability of the USEPA (2017)
373 BBDR model to predict changes in fT4 associated with chronic perchlorate exposure during pregnancy.

374

375 *Greer et al. 2002 – 14 day human controlled perchlorate dosing study*

376 The Greer et al. (2002) study was conducted to establish the dose-response in humans for perchlorate
377 inhibition of thyroidal iodide uptake and any short-term effects on thyroid hormones following
378 exposure for male and female volunteers to perchlorate in drinking water at doses of 7, 20, 100 or
379 500 µg/kg/day for 14 days. The results of this study have previously been relied upon by the USEPA
380 (2005) to derive a reference dose (RfD) and to determine health reference levels (HRLs). The results
381 of this study indicate a decrease in iodide uptake following exposure to a dose of 20 µg/kg/day, but no
382 effect on hormone levels, including fT4 and TSH, at the highest dose tested. A No Observed Effect
383 Level (NOEL) of 7 µg/kg/day was determined based on these results, and an RfD of 0.7 µg/kg/day
384 was adopted, based on NAS recommendations, with the application of an uncertainty factor of 10 for
385 intraspecies variability or sensitive subpopulations.

386 Consistent with the results of the study, our simulations of the adult exposures reported in Greer et al.
387 (2002) with the BBDR model (Table 1) indicated no significant change in fT4 at doses up to 500
388 µg/kg/day. However, predicted concentrations of fT4 are lower than those measured by Greer et al.
389 (2002). The model simulation reported in Table 1 was run with an iodine intake of 90 µg/day, as this
390 was the value USEPA (2017) used in the Greer_test.m script provided with the BBDR model code.
391 However, 90 µg/day is not consistent with the 170 µg/day value USEPA (2017) reports as
392 representing a sufficient intake and USEPA's (2017) documentation does not indicate why a lower
393 value was used for the individuals in the Greer study. Simulation of iodide uptake inhibition (RAIU)
394 appears to over-predict the reduction in uptake compared to measured values, though the qualitative

increasing trend of inhibition with dose behaves appropriately. This discrepancy may result from the low iodine intake chosen by USEPA (2017), or a number of other decisions made in the model revisions, including the reduced Km parameter value. It is unclear why the parameters governing iodide inhibition were altered from previous models that successfully predicted inhibition of iodide in human subjects (Clewell et al. 2007; Merrill et al. 2003; Lumen et al. 2013). Given that iodide inhibition is the obligatory precursor to all downstream effects in the USEPA's proposed mode of action for perchlorate, it would be expected that any changes to the model that lead to reduced accuracy in the prediction of iodide inhibition would be accompanied by substantial support. However, no such support is provided in USEPA (2017) for the changes in the key parameters and the resulting effect on iodide inhibition predictions.

Table 1. Simulation of the Greer et al. (2002) Perchlorate Study

Dose	RAIU (%)		fT4 (pM)	
(µg/kg/d)	Simulated	Measured	Simulated	Measured
0	100	100	10.33	-
7	89	98.2	10.33	-
20	74	83.6	10.32	16.09
100	37	55.3	10.31	15.26
500	11	32.9	10.30	15.44

Braverman et al. 2006 – 6 month human controlled perchlorate dosing study

The Braverman et al. (2006) study was conducted to determine whether prolonged exposure (6 months) of adults to low levels of perchlorate (0.5, 1.0 or 3.0 mg/day) would perturb thyroid function. The study included a small number of individuals (n=13); however, iodine levels were comparable with those of the general population. The authors noted the limitations of the small sample size, but concluded that the results suggested that healthy, euthyroid individuals, with normal levels of iodine intake, can tolerate chronic exposure to perchlorate at doses of up to 3 mg/day (approximately 40 µg/kg/day) without any effects on thyroid function, including inhibition of iodine uptake.

The Braverman et al. (2006) study was simulated as part of the current evaluation using the BBDR model and predicted T3 and TSH levels were compared to the reported measurements (Table 2). fT4

was not compared because it was not clear how to convert the T4 index reported in the study to a concentration and vice versa. As with the Greer et al. (2002) simulation, 90 µg/day was used for iodine intake. Baseline T3 and TSH are similar to the measured values. But, as was seen with fT4, the model fails to predict the observed changes in hormone levels in the adult subjects.

Table 2. Simulation of Braverman et al. (2006) perchlorate study.

Dose	T3 (nM)		TSH (mIU/L)	
(µg/kg/d)	Simulated	Measured	Simulated	Measured
0	2.63	2.49	1.51	1.20
7	2.63	2.51	1.52	1.60
43	2.62	1.77	1.53	2.60

Téllez Téllez et al. 2005a, 2005b – Chilean epidemiological study in pregnant women

Téllez Téllez et al. (2005a, 2005b) reports the results of a longitudinal epidemiological study among pregnant women from three cities in Chile exposed to concentrations of perchlorate as high as 114 µg/L in the public drinking water. The focus of the study was to evaluate maternal thyroid function during pregnancy, neonatal thyroid function and developmental status at birth, and breast milk iodine and perchlorate levels during lactation. The National Academy of Sciences (2005) has reviewed this study in the context of health implications for perchlorate ingestion and concluded this study should be considered in the evaluation of the US experience with perchlorate in drinking water. The total iodine nutrition among this cohort was also noted to be similar to that of US pregnant women (Téllez Téllez et al. 2005a); therefore, this study should be a key consideration in evaluating the relationship between perchlorate exposure, changes in fT4 in pregnant women and developmental status; however, it was not considered in Stage 2 of the USEPA (2017) assessment because it pre-dated the cutoff used by USEPA in their review (2010).

Results from this study indicated no effect on thyroid levels in early pregnancy, late pregnancy, or neonates at birth related to perchlorate in drinking water at concentrations up to 114 µg/L. Given these findings, this study provides a reasonable dataset for validating the impact of high perchlorate exposure concentrations in drinking water on potential changes in fT4 or TSH.

438 We also ran the (USEPA 2017) BBDR model to simulate the Téllez Téllez et al. (2005a, 2005b)
439 drinking water study (Table 3). The BBDR model predictions of fT4 for GW 13-16 are consistent with
440 the negative results of the study, though the predicted concentrations are lower than those observed.
441 This is not a strong validation of the model given the weak trend of changes in hormone levels seen in
442 comparisons to other studies.

Table 3. Simulation of the Téllez Téllez **et al. 2005a, 2005b study of pregnant women exposed to perchlorate via drinking water.**

Dose	**fT4 (pM)**	
(µg/kg/d)	**Simulated**	**Measured**
0.01	9.74	12.5
0.08	9.73	12.2
2	9.69	12.7

443 *Summary: Evaluation of Model Behavior*

444 Our simulations of the Greer et al. (2002) and Braverman et al. (2006) studies with the BBDR model
445 indicate that thyroid hormone levels are relatively insensitive to inhibition of thyroid iodine uptake by
446 perchlorate exposures as high as 7 µg/kg/day. Moreover, our simulations of the Téllez Téllez et al.
447 (2005a, 2005b) study with the BBDR model do not predict an effect on fT4 from exposures to
448 perchlorate at up to 2 µg/kg/d, consistent with the fact that the exposures were demonstrated to be
449 without effect to pregnant women in the study. However, the USEPA (2017) BBDR modeling analysis
450 (Table 4, taken from USEPA 2017)predicted population-level changes in fT4 deficiency during the first
451 trimester at perchlorate exposures nearly an order of magnitude lower (0.3 µg/kg/d) . This
452 discrepancy suggests that the metric used in the USEPA (2017) approach to assess population-level
453 effects of perchlorate, i.e., a 1% or 5% increase the proportion of thyroxinemic mothers in early
454 pregnancy assuming that all individuals have a low (75 µg/day) iodine intake and an inadequate TSH
455 response (pTSH = 0.398 vs. 1), may be overly conservative.

456

Table 4. Summary of Results for the Amount of Perchlorate Needed to Increase the Proportion of Hypothyroxinemic, Low Iodine Individuals by a Defined Percentage (with hypothyroxinemia defined as fT4< 10th Percentile) (USEPA 2017)

Gestational Week	fT4 (pmol/L) at the Hypothyroxinemic Cut Point (i.e. 10th Percentile of 170 µg/day Iodine Intake Group) (Column 1)	Corresponding Percentile in 75 µg/day Iodine Intake Group (Column 2)[a]	Perchlorate Dose (µg/kg/day) Associated with a 1 Percent Increase in Proportion Hypothyroxinemic (Column 3)[a]	Perchlorate Dose (µg/kg/day) Associated with a 5 Percent Increase in Proportion Hypothyroxinemic (Column 4)[a]
12	8.80	48.4	0.4	2.2
13	8.78	47.9	0.4	2.2
16	8.63	52.6	0.3	2.1

[a] Results based on central effect estimates, pTSH in BBDR model set to 0.398

457

458 ***Evaluation of the effect of model assumptions on predicted PODs***

459 In order to assess the potential quantitative impact of some of the uncertainties in the BBDR
460 model, we compared model predictions of percent change in fT4 and TSH for a range of
461 perchlorate concentrations using two alternative parameterizations: (1) the parameterization
462 used by the USEPA (2017) to generate their Table 3, and (2) replacing the equation for
463 HCGREG with the equation for VCHNG (in order to provide an appropriately coupled response
464 to hCG stimulation of thyroidal iodine uptake and thyroid hormone production), and also
465 setting pTSH = 1 (the nominal value, as opposed to the lower-bound value of 0.398 used by
466 the USEPA). The simulations (Table 5) were performed with the model calibrated to either the
467 median population thyroid hormone levels (using the script medset.r) or a low (thyroxinemic)
468 population defined as fT4 < 10th percentile (using the script lowset.r). When predicting the
469 effect of perchlorate exposure on fT4 for the median population there is not a significant
470 difference between the USEPA results and the alternative parameterization; however, the
471 USEPA model parameterization results in more than a factor of 2 greater sensitivity of TSH
472 levels to perchlorate compared to the alternative parameterization. This difference is primarily

473 due to the change in pTSH. On the other hand, when predicting the effect of perchlorate
474 exposure on hypothyroxemic individuals, both fT4 and TSH responses to perchlorate exposure
475 are significantly lower using the alternative parameterization. Thus, the parameters that were
476 altered in the recent revision of the model (VCHNG, HCGreg, pTSH, KmNiS_p) increase the
477 predicted effect on thyroid hormone levels compared to the expected response with the well-
478 validated precursor event of iodide inhibition. The sensitivity of the prediction to changes in
479 these parameters, and the disconnect between the prediction of iodide inhibition and thyroid
480 hormone levels, calls for better justification – and evaluation – of the given parameter values.

Table 5. Predicted fT4 and TSH Concentrations at Various Doses of Perchlorate for 75 µg/day Iodine Intake

Perchlorate Dose (µg/kg/day)	fT4 (pmol/L) (% Change from 0 Dose)				TSH (mIU/L) (% Change from 0 Dose)			
		USEPA[0]	VCHNG + pTSH[1]	VCHNG + pTSH[1]		USEPA[0]	VCHNG + pTSH[1]	VCHNG + pTSH[1]
	Population	Median	Median	Low	Population	Median	Median	Low
0	Absolute	8.6	9.9	7.5	Absolute	2.2	1.5	3.0
1	Percent Change	-0.74	-0.8	-0.31	Percent Change	3.3	1.4	1.9
2		-1.5	-1.6	-0.61		6.6	2.7	3.8
3		-2.1	-2.3	-0.9		10	4.1	5.7
4		-2.8	-2.9	-1.2		14	5.5	5.7
5		-3.4	-3.5	-1.5		17	6.9	7.7
10		-6.2	-6.2	-2.8		36	14	19

[0] Results using pTSH = 0.398

[1] Results using HCGREG replaced with VCHNG, and pTSH=1

481 **Review of Literature Linking BBDR Results to Neurodevelopment Outcomes**

482 Chapter 5 of USEPA (2017) focuses on the SAB's recommendation to "Identify literature and conduct
483 analyses to support the model outputs for the downstream steps" from the BBDR's predicted changes
484 in thyroid hormones following exposure to perchlorate. Specifically, Chapter 5 was developed to
485 present the process USEPA (2017) used to identify literature to support the draft approach for
486 derivation of the MCLG for perchlorate. USEPA (2017) states, "Based on the recommendations of

previous peer review panels, USEPA assumed that changes in thyroid hormone levels would be expected to lead to neurodevelopmental outcomes", and because of this assumption, a complete systematic review of the body of literature on this topic was not performed. Instead, a "focused review of the published literature" was conducted.

The approach is inconsistent with recent recommendations from the National Research Council (NRC 2014) regarding systematic review and evidence integration. These recommendations are currently being incorporated into the USEPA's Integrated Risk Information System (IRIS) process and USEPA has recently released scoping and problem formulation materials for several new Integrated Risk Information System (IRIS) assessments, including ethylbenzene (USEPA 2014a), and naphthalene (USEPA 2014b). The approach applied in these assessments is intended to follow recommendations provided by the National Research Council (NRC 2013). While development of MCLGs are not part of the IRIS process, the application of systematic review principles in the identification of studies to define the relationship between fT4 and neurodevelopmental effects, is needed. The application of these principles would not only assist in defining the highest quality studies to address a specific research question, they also provide a way to integrate all of the available evidence for the specific research questions raised by the SAB. Systematic reviews include the formulation of a specific question to be addressed and developing a protocol that specifies the methods that will be used to address the question. While a broad research question can lead to a large systematic review, if the research question is limited, such as in the case of perchlorate, then the systematic review becomes more focused.

For the USEPA (2017) draft MCLG approach, a systematic review question could have been easily developed based on the SAB recommendation (i.e. "Identify literature and conduct analyses to support the model outputs for the downstream steps") and the protocol would simply be focused on the methods for conducting the systematic review to address this very focused systematic review question in a transparent manner. Transparency being defined by USEPA as "sufficient information will be available to understand the scientific rational behind decisions, as well as, reproduce methods used to identify and evaluate data". However, in the case of the literature identified for consideration in the draft MCLG approach for perchlorate, a well-defined protocol for all steps of the process has not been developed and therefore is inconsistent with the recommendations of the NRC (2013):

> *"A priori decisions and a predefined protocol are critical during the systematic review process (Berlin and Colditz 1999; Dickersin 2002); the protocol should describe the following steps: the research question, the search strategy and data sources, the study inclusion and exclusion criteria, the data to be abstracted and derived from the original studies (such as sample size, exposure and outcome assessment methods, and confounders evaluated), the criteria and methods for pooling effect estimates and measures of variability among studies. Systematic reviews and meta-analyses need to be replicable; other investigators following the same steps should be able to identify the same articles, abstract the same data, and reach similar conclusions."*

At each step of the process for identifying studies for use in the development of the MCLG approach for perchlorate, a detailed set of criteria is needed. For example, if decisions are made to include or exclude any studies, there should be very detailed criteria indicating why studies were included or excluded and it should be specified prior to the initiation of the literature searching process. The criteria for each step should be described in such a way that an independent reviewer could use it to replicate the results of the literature search and review; however, there are several areas in the USEPA (2017) draft MCLG approach for perchlorate where this level of detail is lacking, making it difficult for an independent reviewer to replicate the results.

Systematic Review Research Questions

An overall hypothesis or systematic review research question should be developed that is based on the SAB recommendation to clarify the focus of the review and the linkage between altered maternal fT4 (as predicted by the BBDR model) and the potential for adverse neurodevelopmental effects in offspring. Some additional explanation as to how USEPA arrived at the specific neurodevelopmental outcomes of concern should be provided.

Searching the Published Literature

While the literature search key words are presented in the USEPA (2017) report, there is a lack of explanation as to the reasoning behind the focus on the outcome of concern. The research question should be used to develop the literature search. The major points used or considered in developing

544 the literature search strategy should be presented. In addition, there should be a detailed explanation
545 of the criteria used to screen the literature search results. Furthermore, USEPA (2017) does not
546 report the details of the literature search results. For each search string reported in Table 9 of the
547 USEPA (2017) report, a total number of citations identified should be reported. In addition, the
548 criteria used to screen the original search results should be clearly reported in the document.
549 Essentially, each step of the literature search and review should be reported in such a way that any
550 independent party could easily reproduce the results reported in Chapter 5 of USEPA (2017). The lack
551 of this type of information does not allow the reader to determine if any key studies may have been
552 removed from consideration.

553 *Literature Screening Approach and Selection of Key Studies*

554 USEPA (2017) states that a 3 step approach was used to identify studies for consideration in the
555 development of the approach for derivation of the MCLG for perchlorate. The approaches utilized by
556 USEPA (2017) to identify the epidemiological studies for this evaluation were strictly focused on the
557 appropriateness of the quantitative data for consideration in combination with the output of the BBDR
558 model. Group 2 (studies with categorical analyses only) and Group 3 (studies with analyses not
559 directly compatible with BBDR output) studies were apparently eliminated from consideration in the
560 assessment. While not directly compatible with BBDR modeling output, it is possible that these
561 studies may provide information important in understanding the potential relationship between
562 changes in thyroid hormones and the potential for neurodevelopmental effects, as well as potential
563 key confounders.

564 While 15 studies were identified in Group 1, only 5 of these were determined by USEPA to include
565 analyses that could be used to connect the results of the BBDR model to incremental changes in
566 adverse neurodevelopmental effects. A clearly defined set of inclusion and exclusion criteria should be
567 provided to clearly convey to the reader why the other 40 studies in Groups 1, 2, and 3 were not
568 considered. In addition, studies that provide no evidence of an inverse relationship between
569 perchlorate exposure and serum thyroid function (e.g. Ghassabian et al. 2014; Modesto et al. 2015;
570 Moleti et al. 2016; Noten et al. 2015) should also be considered to not only understand why these
571 results are in contrast to the potential research question, but also that the overall weight of evidence
572 can be determined. It is possible that the majority of studies provide evidence that critical factors that

573 are not reported in some of the available studies may explain the reported changes in serum thyroid
574 function.

575 *Assessment of Study Quality and Risk of Bias*

576 According to recent recommendations from the National Research Council (NRC 2014), the National
577 Toxicology Program's (NTP) Office of Health Assessment and Translation (OHAT) method for the
578 assessment of study quality and risk of bias of the literature (NTP 2015) is one method that should be
579 considered for qualitative and quantitative assessments. "An assessment of study quality evaluates
580 the extent to which the researchers conducted their research to the highest possible standards and
581 how a study is reported. Risk of bias is related to the internal validity of a study and reflects study-
582 design characteristics that can introduce a systematic error (or deviation from the true effect) that
583 might affect the magnitude and even the direction of the apparent effect" (NRC 2014). Each study
584 meeting inclusion criteria in Group 1, 2, and 3, should be evaluated against a predetermined set of
585 study quality and risk of bias criteria and the results of this evaluation should be presented in the
586 perchlorate MCLG approach report.

587 Uncertainties Critical to Characterizing Changes in Thyroid Hormone Levels in Pregnant Women
588 Associated with Neurodevelopmental Changes in Offspring

589 The draft MCLG approach presented in USEPA (2017) to predict doses of perchlorate that would result
590 in per unit changes in neurodevelopmental measures, is, as noted by USEPA (2017), "…dependent
591 upon predictions from the BBDR model, the derivation of the distribution of fT4, and the evaluations of
592 the relationship between fT4 and neurodevelopment. Each of these steps has inherent uncertainties
593 associated with it."

594 A major source of uncertainty is related to the five studies in Group 1 with data that could be used to
595 quantitatively describe the relationship between thyroid hormone levels in early pregnancy and
596 changes in neurodevelopment (Pop et al. 1999, 2003; Finken et al. 2013; Korevaar et al. 2016;
597 Vermiglio et al. 2004). None of these five studies relied upon data from US populations or have been
598 demonstrated to have iodine intake similar to US populations. Yet according to the American Thyroid
599 Association (Alexander et al. 2017), the reference range of both TSH and fT4 in pregnant women
600 varies depending upon ethnicity. While two studies in Group 1 focused on population groups within

601 the United States, neither were considered for the model because T4 and not fT4 was measured in the
602 pregnant females (Oken et al. 2009) and the relationship between fT4 and neurodevelopment was
603 evaluated in late pregnancy and did not reach statistical significance (Chevrier et al. 2011). USEPA
604 (2017) (Section 6.5.1) states "there is no reason to believe that the impact of fT4 on
605 neurodevelopment would differ by country, unless there is a substantial difference in iodine intake".
606 While USEPA (2017) does make an effort to evaluate changes in iodine intake in women from various
607 populations, including the US, there are not substantial data reported in the peer-reviewed literature
608 to validate the conclusions that the impact of fT4 on neurodevelopment would differ by population or
609 uncertainty in iodine intake levels would have an impact on the derivation of the MCLG. This is
610 inconsistent with data from the American Thyroid Association (Alexander et al. 2017) that suggest
611 variability in the distribution of thyroid hormone levels across populations and even within ethnicities
612 within a single population.

613 USEPA (2017) also notes that all five studies used for quantitative analysis relied on a one-time fT4
614 level during pregnancy (Section 6.5.5). The influence of changes in maternal fT4 on fetal brain
615 development is likely greatest during early pregnancy. The variability in maternal fT4 levels during
616 pregnancy and the lack of measurement of fT4 at time points throughout pregnancy in the studies
617 provides a substantial data gap and lack of information needed to validate some of the assumptions
618 relied upon in the development of the BBDR current model as well as the resulting predictions of the
619 model. As stated in USEPA (2017),

620 *"Circulating T3 and T4 levels in an individual are maintained within a narrow range by*
621 *a negative feedback loop with TSH from the pituitary and TRH from the hypothalamus*
622 *that operates around a "set-point." This set-point is different from individual to*
623 *individual, which generates a population variance in blood levels of thyroid hormone*
624 *that is considerably broader than the individual variance (Andersen, Pedersen, Bruun,*
625 *& Laurberg 2002). Therefore, in euthyroid individuals, serum T4 and T3 fluctuate*
626 *within a fairly narrow range (about 10% of the population variance), maintained by*
627 *the negative feedback relationship with serum TSH from the pituitary gland. This*
628 *normal variation creates a situation where single measures of free or total T4 and TSH*

629 *are a somewhat imprecise measure of an individual's average T4 and TSH*
630 *concentrations (Andersen et al. 2002)."*

631 Several other areas of uncertainty are also highlighted by USEPA (2017). Specifically, USEPA
632 (2017) noted that none of the five studies carried forward provided iodine intake levels
633 (Section 6.5.3), which adds significant uncertainty to the estimates. Three of the 5 studies
634 (Pop et al. 1999, 2003; Vermiglio et al. 2004) also have populations of less than 30
635 decreasing the statistical power of the studies (section 6.5.4) relied upon for establishing the
636 relationship between changes in fT4 and neurodevelopmental changes. USEPA (2017) also
637 noted uncertainties in regard to the analytical methods used to evaluate fT4 levels and while
638 approaches are being introduced to standardize analytical methods, results at different time
639 points and from different countries may vary considerably due to differences in analytical
640 procedures (USEPA 2017). USEPA (2017) also notes that "there is uncertainty regarding the
641 true fT4 levels at various percentiles in the distribution around the median output from the
642 BBDR model. This is exemplified by the fact that in this analysis larger unit changes are being
643 seen with increasing percentiles of fT4 in most analyses." Finally, other confounders such as
644 iron deficiency were not considered in the analysis. Iron deficiency in pregnant mothers,
645 which is noted in approximately 18% of pregnant women in the US (Cantor et al. 2015), may
646 also be associated with hypothyroxinemia (Yu et al. 2015) and failing to directly account for a
647 relationship between iron deficiency and hypothyroxinemia may introduce an uncertainty into
648 this analysis.

649 While all these uncertainties are noted by USEPA (2017), there is no attempt to adjust the
650 draft MCLG approach in any way to account for these uncertainties. Many of these, especially
651 confounders such as iron deficiency in the study population and a lack of information on iodide
652 intake, can have a significant effect in characterizing changes in thyroid hormone levels
653 associated with changes in neurodevelopmental outcomes. In the absence of adequately
654 accounting for these uncertainties, it is difficult to have confidence that BBDR model
655 predictions of small changes in a specific thyroid hormone (e.g. fT4) may accurately predict
656 the potential for neurodevelopmental effects.

The inadequacy of the USEPA (2017) literature review is substantiated by the comments of the External Peer Review for USEPA's Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water (Versar 2018). Comments regarding the USEPA (2017) literature search included:

- "The literature search produced ten studies (that assessed maternal serum FT4 concentrations as a continuous measure which did not observe an adverse effect on offspring neurocognition), as well as those in Group 2 that assessed serum FT4 as categorical measures. Although their inclusion may not necessarily be recommended in the final model, comparison of the estimated effects on the various neurocognitive outcomes with and without these may indeed inform the degree of uncertainty inherent in the present model. Several of the studies in Group 2 were able to demonstrate significant adverse outcomes (Berbel 2009 as one excellent example), and also their more global nature would help support the generalizability of the present model."
- "Excluding these studies lessens the power of the total sample size and thus the ability to detect an association between maternal hypothyroxinemia and any of the offspring outcomes, but provides what may be a somewhat exaggerated estimate of the potential adverse effects of perchlorate exposure. This approach is more conservative, to which there are pros and cons of doing so, toward derivation of a perchlorate MCLG. With this approach, the goal is to minimize exposure to the lowest perchlorate concentration associated with any number of adverse outcomes. I would favor the more liberal public health approach, which is inclusion of all available studies, whether they are positive or negative. Although the perchlorate MCLG may be higher, this latter approach would be consistent with using all available evidence to improve the scientific rigor of the proposed study question."

The peer reviewers also suggested a number of additional peer-reviewed studies that they felt should have been considered to inform BBDR modeling of the quantitative relationship between thyroid hormone levels and neurodevelopmental outcomes:

- Bárez-López S, Jesus-Obregon M, Bernal J, Guadaño-Ferraz A. 2017. Thyroid Hormone Economy in the Perinatal Mouse Brain: Implications for Cerebral Cortex Development. Cerebral Cortex, 28(5): 1783-1793.
- Bath S, Steer C, Golding J, Emmett P, Raymen M. 2013. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). The Lancet, 382(9889): 331-337.
- Bernal J. 2017. Thyroid hormone regulated genes in cerebral cortex development. Journal of Endocrinology, 232(2): R83-R97.
- Casey B, Thom E. 2017. Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. The New England Journal of Medicine, 377(7): 701.
- Casey B, Thom E, Peacemann A, Varner M, Sorokin Y, Hirtz D, Reddy U, Wapner R, Thorp J, Saade G, Tita A, Rouse D, Sibai B, Iams J, Mercer B, Tolosa J, Caritis S, VanDorsten JP. 2017. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. The New England Journal of Medicine, 376: 815-825.
- Endendijk J, Wijnen H, Pop V, van Baar A. 2017. Maternal thyroid hormone trajectories during pregnancy and child behavioral problems. Hormones and Behavior, 94: 84-92.
- Hales C, Taylor P, Channon S, Paradice R, McEwan K, Zhang L, Gyedu M, Bakhsh O, Muller I, Draman M, Gregory J, Dayan J, Rees D, Ludgate M. 2018. Controlled Antenatal Thyroid Screening II: effect of treating maternal sub-optimal thyroid function on childhood cognition. The Journal of Clinical Endocrinology and Metabolism, 103(4): 1583-1591.
- Lazarus J, Bestwick J, Channon S, Paradice R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George L, Perona M, Dall'Amico D, Parkes A, Joomun M, Wald NJ. 2012. Antenatal Thyroid Screening and Childhood Cognitive Function. The New England Journal of Medicine, 366: 493-501.
- Taylor PN, Okosieme OE, Murphy R, Hales C, Chiusano E, Maina A, Joomun M, Bestwick JP, Smyth P, Paradice R, Channon S, Braverman LE, Dayan CM, Lazarus JH, Pearce EN. 2014. Maternal Perchlorate Levels in Women with Borderline Thyroid

Function During Pregnancy and the Cognitive Development of Their Offspring: Data from the Controlled Antenatal Thyroid Study. The Journal of Clinical Endocrinology & Metabolism, 99(11): 4291-4298.

In the draft MCLG approach, USEPA (2017) focused on five studies that evaluated the relationship of maternal fT4 and several neurodevelopmental endpoints (IQ, mental development index (MDI), psychomotor development index (PDI), standard deviation of reaction time), based on measurements of fT4 during early pregnancy. Results from previous studies have provided the basis for No Observed Effect Levels (NOELs) for health effects of perchlorate in the development of Reference Doses and currently recommended Health Reference Levels (HRLs), including Greer et al. (2002) in which adult men and women were exposed to perchlorate in drinking water at doses of 0.007, 0.02, 0.1, or 0.5 mg/kg/day for 14 days demonstrated a NOEL for perchlorate inhibition of radioiodide uptake by the thyroid NIS following exposure to 7 µg/kg/day. The point of departure from the Greer et al. (2002) study represents a perchlorate level that precedes the inhibition of iodine uptake by the thyroid. The NAS RfD developed based on the point of departure (POD) from this study is a deviation from the Agency's traditional approach of using a No Observed Adverse Effect Level (NOAEL) for regulatory actions. The NAS's use of a No Observed Effect Level (NOEL) is based on "using a nonadverse effect that is upstream of the adverse effect [which] is a more conservative and health protective approach".

While these studies have not been conducted in pregnant women (the population of interest for the draft MCLG approach), as noted by in USEPA (2017):

> *"…the BBDR model predicts very little difference in non-pregnant and first-trimester response to perchlorate. This likely occurs because the half-life of (organified) iodine in the adult thyroid is around six months, hence the availability of thyroidal iodine in the first trimester pregnant woman is determined to a very large extent by her nutrition and perchlorate exposure several years preceding pregnancy."*

This suggests that a comparison of the current modeling results to those from studies conducted in adults should provide insight into the predictions of the model and the conclusions regarding the changes in thyroid hormone levels that may result in neurodevelopmental effects.

742 The current draft approach for deriving the MCLG assumes any exposure to perchlorate reduces fT4 to
743 some extent (p. 3-17 of USEPA 2017). In addition, linear regression analyses conducted to evaluate
744 the relationship between changes in fT4 and neurodevelopmental effects further assumes any change
745 in fT4 results in some risk of neurodevelopmental effects. These assumptions are in contrast to the
746 results from Greer et al. (2002) in which exposures to perchlorate were as high as 500 µg/kg/day and
747 no impact on thyroid hormone levels was observed. This was true for both men and women. In
748 addition, in a study conducted by Braverman et al. (2006), 6 months of exposure to perchlorate in
749 capsules at doses up to 3 mg/day (approximately 40 µg/kg/day) was reported to have no effect on
750 thyroid function, including inhibition of thyroid iodide uptake as well as serum levels of thyroid
751 hormones, TSH, and Tg in a small group of volunteers.

752 USEPA (2017) notes (p. 6-16) that from results of the literature review, it appears the relationship
753 between maternal fT4 and fetal brain development has a temporal relationship, with this influence
754 likely being greatest in early pregnancy (i.e. prior to mid-gestation). The focus of the evaluation is on
755 gestational weeks 12, 13, and 16, where the mother's fT4 levels will have the greatest impact on the
756 fetus. This should allow for comparison to the model results in pregnant women to results from
757 previous studies focused on identification of perchlorate concentrations that would impact fT4 levels in
758 adult women, such as the Greer et al. (2002) study.

759 Based on the BBDR model predictions, USEPA (2017) estimates that a perchlorate dose of 0.3-0.4
760 µg/kg/day would result in a 1% increase in the proportion of the population with hypothyroxinemia
761 and a perchlorate dose of 2.1-2.2 µg/kg/day would result in a 5% increase in proportion of the
762 population with hypothyroxinemia. These modeling results suggest a potential for a significant change
763 in thyroid hormones, as well as adverse effects on neurodevelopment at doses of perchlorate exposure
764 for which there is evidence that decreases in fT4 are not observed. Based on the mode of action
765 proposed by USEPA (2017), decreases in fT4 and increases in TSH would be prerequisite steps for the
766 potential for neurodevelopmental effects. These changes in hormone levels are not observed in the
767 Greer et al. (2002) study following exposure up to 500 µg/kg/day. The draft MCLG approach suggests
768 population changes in fT4 would be observed that would shift the proportion of pregnant women that
769 would be hypothyroxinemic at doses of perchlorate below the previously defined NOEL (7 µg/kg/day).

Table 6 (Table 39 of USEPA 2017) provides the predicted dose of perchlorate per unit change in neurodevelopmental measure for low iodine intake individuals. Those for IQ are approximately at or above (6.5 – 45 µg/kg/day) the NOEL from Greer et al. (2002) and are associated with decreases in fT4 of 4.3 to 18.7%. The doses associated with other neurodevelopmental endpoints are 1.7 to 3.0 µg/kg/day and are associated with decreases in fT4 of 1.3 to 2.4%. These percent changes in fT4 are very small and considering the potential uncertainty and variability in measuring fT4 levels, there is a lack of evidence that such small changes in fT4 will result in clinical observations. Reference ranges for fT4 are 0.9 – 2.5 ng/dL in infants (0-5 days) and 0.9 – 1.7 ng/dL in adults (> 20 yrs) (https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8725). Thus, for an adult, at the low end of the reference range, we would expect a change from 0.900 to 0.878 ng/dL, a value that given the number of significant figures in the reference value would not be measurable. The dose of perchlorate estimated to result in a 1% or 5% increase in the proportion of hypothyroxinemic pregnant women is even lower, ranging from 0.3 to 2.2 µg/kg/day. USEPA (2017) findings are contrary to multiple studies in adults and pregnant women (Greer et al. 2002; Braverman et al. 2006; Téllez Téllez et al. 2005a, 2005b) provide robust evidence that no impact on iodine uptake or thyroid hormone levels would be expected at these dose levels. Based on the mode of action proposed by USEPA (2017), these precursor impacts are necessary to generate the neurodevelopmental effects derived from the BBDR model.

Table 6. Predicted Dose of Perchlorate per Unit Change in Neurodevelopmental Measure for Low Iodine Intake Individuals based on Central Effect Estimates at the Median fT4 level (USEPA 2017)

Study	Endpoint	ΔfT4 in pmol/L (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)	Dose of perchlorate per unit change in endpoint (µg/kg/day)[a]
Korevaar et al. (2016) Quadratic	IQ	-1.08 (12.2%)	23
Korevaar et al. (2016) USEPA Independent Analysis: Bivariate	IQ	-0.98 (11.1%)	20
Korevaar et al. (2016) USEPA Independent Analysis: Multivariate	IQ	-1.66 (18.7%)	45
Vermiglio et al. (2004)	IQ	-0.37 (4.3%)	6.5
Pop et al. (2003)	MDI	-0.15 (1.7%)	2.2
Pop et al. (2003)	PDI	-0.12 (1.3%)	1.7
Pop et al. (1999)	PDI	-0.12 (1.3%)	1.7
Finken et al. (2013)	SD of Reaction Time	-0.21 (2.4%)	3.0
BBDR model (USEPA 2017)	1% or 5% increase in proportion of hypothyroxinemic pregnant women[b]	1% or 5%	0.3 – 0.4[c] [1%] 2.1 – 2.2[c] [5%]

[a] Based on the regression analysis for the range of fT4 data within each study. Central beta estimates of the low iodide intake population (= 75 µg/day) are presented.

[b] Hypothyroxinemia defined as fT4 < 10th percentile

[c] Range based on gestational week used to perform the analysis (12 to 16 weeks).

788

DISCUSSION

A critical review of the (USEPA) 2017 report entitled "Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water", as well as the BBDR model that was proposed for use in derivation of the MCLG, was conducted. Overall, conducting this review and assessment of the BBDR model was beset by multiple challenges and the effort highlighted a number of uncertainties in the use of the model. The main challenges that the review presented were due to the complexity of the BBDR model itself. The co-authors of this review, who are widely considered to be experts in the area of PBPK and BBDR model development, found it difficult to evaluate the complex interactions of model parameters and their relationship to the predictions of the model. In our efforts to reproduce simulations provided in USEPA (2017), it was noted that instructions for running the model for different scenarios, and documentation of the rationale for the model parameter values associated with them, were sometimes inadequate; this deficiency, which is inevitable in a complex model, was exacerbated by the number of code scripts required to set the parameters used to generate the various results in the document. As a result, the ability to independently verify all aspects of the model were impeded by uncertainties associated with the steps necessary to reproduce figures and tables in the report, or to perform comparisons of model predictions to data for alternative exposure scenarios or studies.

As suggested by C.A.R. Hoare in his 1980 ACM Turing Award Lecture: "There are two ways of constructing a software design: One way is to make it so simple that there are obviously no deficiencies and the other way is to make it so complicated that there are no obvious deficiencies." By their nature, BBDR models are seldom simple; to the extent that BBDR models attempt to describe complex biological systems they will inherently be difficult to comprehend. The criticisms of the perchlorate PBPK model in this case study are not meant to suggest that the model is incorrect or un-useful, and they should not be taken as criticisms of the utility of BBDR modeling in general. Used appropriately, BBDR models can provide important information for better risk assessment decision-making. The issue that needs to be addressed in each case is whether a BBDR model is fit for the intended purpose of using it in the risk assessment.

The first use of PBPK modeling in risk assessments dates back to the 1980s (USEPA 1987) and yet the application of PBPK modeling to replace default dosimetry remains controversial, primarily due to

818 concerns regarding model uncertainty. To address these concerns, the OMB (2007) memorandum on
819 risk analysis recommended the presentation of results from multiple dose-response approaches to
820 provide a more robust risk characterization. In this scenario, a fit-for-purpose BBDR model can
821 provide information on the most scientifically plausible risk estimate for comparison with the results of
822 default approaches (Clewell et al. 2008). Consistent with this OMB recommendation, one focus of our
823 evaluation was determining how the results of the BBDR modeling could inform the likelihood that the
824 current perchlorate guideline (USEPA 2005), which is based on inhibition of thyroidal iodine uptake in
825 adults, is also protective of concerns regarding neurodevelopmental effects of perchlorate. This
826 question is discussed in the Conclusion.

827 The current BBDR model that was relied upon for the USEPA (2017) draft approach is an extension of
828 previous models that have been validated and published in the peer-reviewed literature (Clewell et al.
829 2007; Merrill et al. 2003; Lumen et al. 2013). Similar values for key parameters have been
830 successfully used across the previous models, yet changes were made in the current model or new
831 parameters added (e.g. VCHNG, HCGreg, pTSH, KmNiS), often with little or no evidence or
832 justification provided to support these revisions in the USEPA (2017) documentation. Additional
833 support for these changes will be needed to provide validation of the current revisions to the BBDR
834 model and to provide confidence in the predictions of changes in fT4 made by the model.

835 Certainly, confidence in the BBDR model predictions is undermined by the model's inability to simulate
836 the results from the Steinmaus et al. (2016) study. In Appendix B of USEPA (2017), a comparison of
837 the predicted changes in both fT4 and TSH from the BBDR model were compared to the results
838 reported by Steinmaus et al. (2016) (reproduced in Figure 6). The Steinmaus et al. (2016) study was
839 conducted to evaluate the potential for perchlorate exposure to impact thyroid hormone levels in
840 pregnant women in San Diego. This comparison clearly highlights the differences between the model
841 predictions and those from a published study. The baseline BBDR simulations with normal iodine
842 intake (170 µg/day) demonstrate no change in fT4, which is consistent with other studies in which no
843 impact on fT4 has been observed at doses up to 7 µg/kg/day (Greer et al. 2002; Braverman et al.
844 2006). The BBDR model underpredicted changes in fT4, even in the scenario with low dietary iodine
845 intake (75 µg/day), when compared to the changes reported by Steinmaus et al. (2016). This
846 discrepancy calls into question the ability of the model to predict changes in fT4 associated with

847 perchlorate exposure. In particular, the proposed MCLG approach depends on model predictions of
848 small changes in fT4 as low as approximately 1% (Table 6) being associated with unit changes in
849 neurodevelopmental endpoints. Predictions of this precision would require a level of model precision
850 that has not been demonstrated by comparisons to existing data.

851 Many of the changes in fT4 that are predicted by the draft MCLG approach to estimate impact on the
852 population distribution of fT4 and therefore result in per unit changes in neurodevelopmental
853 outcomes are small percent changes (some as low as a 1.3-4.3% change). This would appear to
854 suggest that the extended version of the BBDR model has a capability to estimate small changes in
855 fT4 with a level of precision that is not demonstrated by any adequate validation. In fact, BBDR model
856 predictions of fT4 underpredict observed data in human studies (Tables 1 and 3) by as much as 25-
857 35%. Moreover, considering the variability of fT4 in the populations of interest, there is uncertainty as
858 to whether these slight changes could be measured clinically, considering the greater impact of iodine
859 intake on hormone levels. Considering the lack of data to support critical parameters and
860 assumptions in the model, as well as the impact of the variability of iodine intake on model
861 predictions, it seems crucial that validation of the BBDR model by comparison with observed data be
862 used to provide confidence in the predictions of the BBDR model. However, the BBDR model clearly
863 fails the only comparison that has been conducted (Figure 6), with the BBDR model predictions falling
864 outside the bounds of the statistical confidence limits estimated for the Steinmaus et al. (2016)
865 relationship between perchlorate dose and fT4. Each of the components of the BBDR model combined
866 result in compounded uncertainty in the modeling results.

867 Until additional data are available to validate current extensions of the BBDR model to the pregnant
868 woman, the Greer et al. (2002) and Braverman et al. (2006) studies provide the critical information in
869 determining concentrations of perchlorate that do not result in significant inhibition of iodide uptake
870 and, therefore, impacts on fT4. Based on recommendations from the National Academy of Sciences
871 (2005), points of departure provided by these studies used in combination with uncertainty factors
872 were considered to be protective of sensitive subpopulations, this approach has previously been relied
873 upon to support guidelines for perchlorate in drinking water under the Safe Drinking Water Act (USEPA
874 2008), and has also been used more recently by JECFA (2011) and EFSA (2014) in their regulation of
875 perchlorate.

CONCLUSIONS

We applaud the USEPA for the application of a BBDR model in their draft MCLG approaches, as these models integrate the available science for a compound of interest. However, while the hormone component of the model is a scientific improvement in terms of incorporating the available biology, there is a lack of data to provide critical validation in multiple steps of the proposed approach and to support several assumptions/parameters within the BBDR model. In particular, while no major structural defects in the USEPA (2017) BBDR model were identified, there are a number of uncertainties in the model parameterization that call into question its use for predicting very small changes in clinical hormone values, such as a 1% change in fT4 (Tables 4-6) While the model prediction for 1% change in fT4 (0.3-0.4 µg/kg/day) would yield a POD lower than the USEPA (2005) RfD, that level of precision is a not supported by the comparison of the model predictions with available data. Nonetheless, the consistency of the model-predicted PODs based on the epidemiological endpoints (Table 6), and the relationship of these results with previous risk assessments based on biologically sound precursors (iodide inhibition in thyroid), indicate that the interim health standard would be sufficiently protective against the developmental neurological endpoints of concern, as illustrated in Figure 7, which compares the point of departure from the USEPA (2005) IRIS assessment with the PoDs calculated by the BBDR model in the USEPA (2017) report (Table 6). The USEPA (2005) RfD (red bar) is protective for all of the endpoints from epidemiological studies and is consistent with a change in population fT4 levels of less than 5%.

Beginning with the initial risk characterization for perchlorate (USEPA 2002), the fundamental underpinning of the agency's risk assessment approach has been the use of an obligatory precursor as a conservative basis for protecting against downstream health effects. As elaborated in the original documentation (USEPA 2003), the effects of perchlorate are mediated by the inhibition of thyroidal iodine uptake by perchlorate. Unless perchlorate concentrations in the blood are sufficient to disrupt iodine uptake, there is no plausible basis for suggesting an effect of perchlorate on thyroid hormone homeostasis or subsequent events leading to developmental or (in the rat) carcinogenic effects. The recent studies suggesting a relationship between perchlorate exposure and decreased fT4 do not impeach this causal relationship. Therefore, until the significant uncertainties in the current BBDR

model and draft MCLG approaches can be addressed, USEPA should continue to rely on the RfD approach based on inhibition of thyroidal iodine uptake (USEPA (2005), as recommended by the National Academy of Sciences (2005) for any further regulatory action. The USEPA (2005) RfD includes an intraspecies uncertainty factor of 10 "to protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency." None of the predictions of the BBDR model suggest that this uncertainty factor is inadequate.

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1141 Figure 1. Mode-of-action model for perchlorate toxicity proposed by the USEPA (2002).
1142 Inhibition of iodide uptake in the thyroid by perchlorate is an obligatory precursor for all
1143 downstream cancer and noncancer endpoints, including neurodevelopment.

1144 Figure 2: Structure of the Early Pregnancy BBDR (USEPA 2017)

1145 Figure 3: Variation in free T4 (fT4 in early pregnancy (as reported in USEPA 2017))

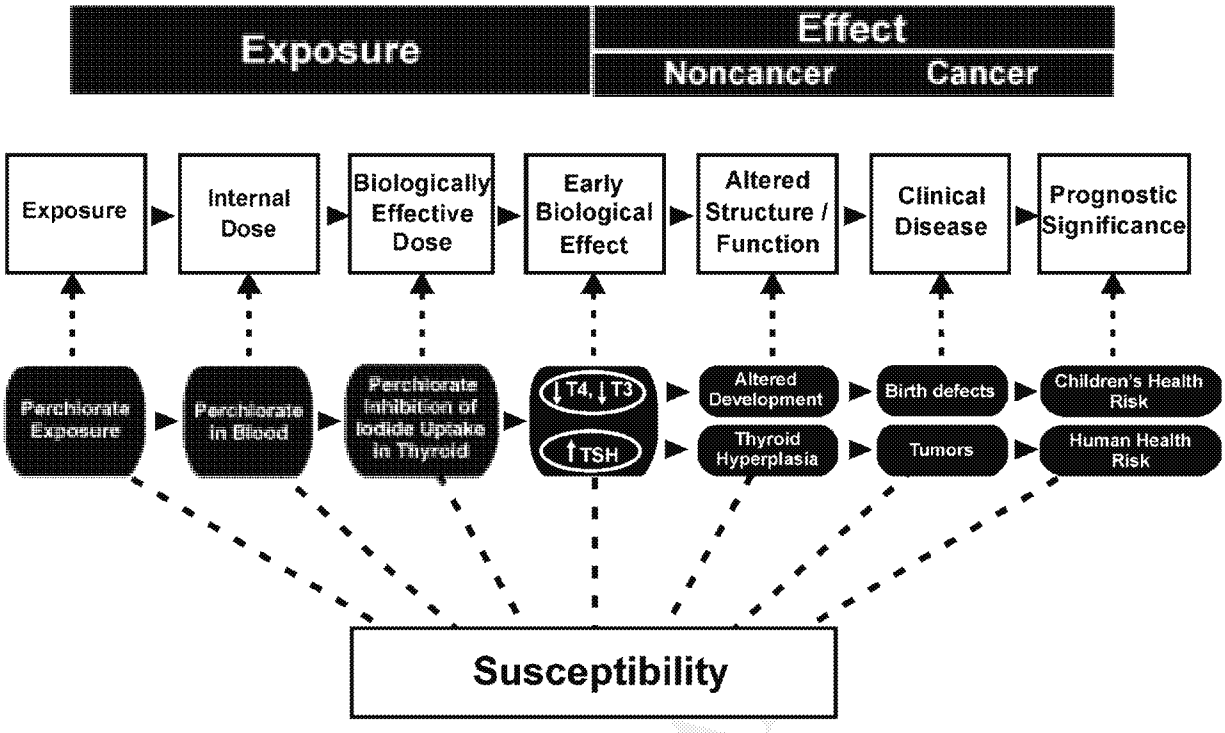
1146 Figure 4, Comparison of parameters controlling hCG-dependent changes in thyroidal uptake
1147 (VCHNG, green) and thyroid hormone production rate (HCGREG, purple) in the BBDR model as
1148 a function of gestational age. Despite the fact that both parameters are dependent upon hCG
1149 levels, the predicted trends across gestation are not consistent.

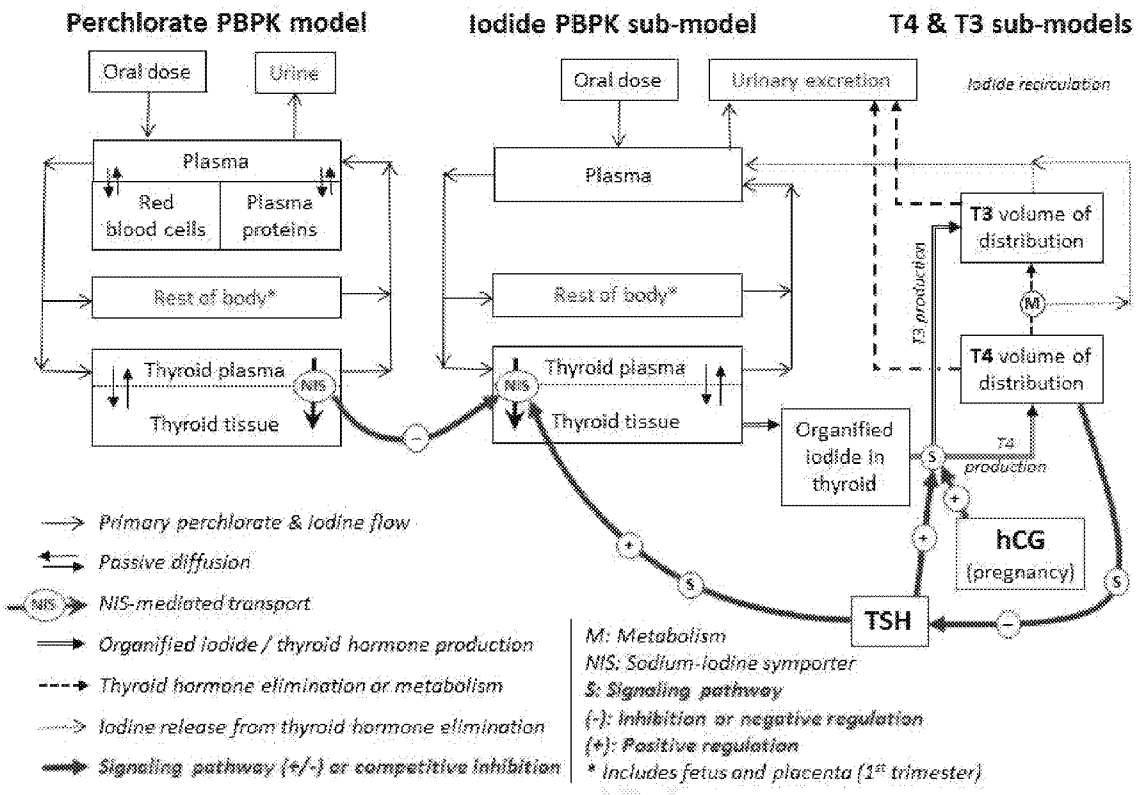
1150 Figure 5. Panel a: Model predictions for free T4 (fT4) in non-pregnant women as a function of
1151 iodine intake compared to data from NHANES 2007-2012 (USEPA 2017). Panel b: Underlying
1152 NHANES data without model predictions. Note the lack of evidence for any correlation
1153 between iodine intake and fT4 in the NHANES data in the range from 20 to 90 µg/d, in
1154 contrast to model predictions.

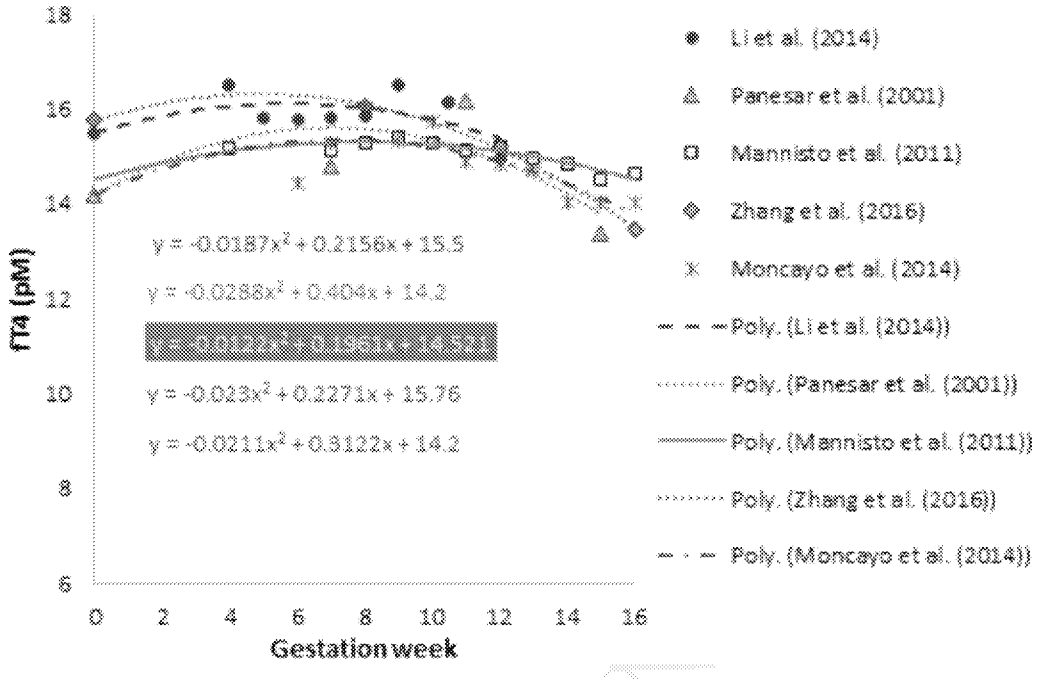
1155 Figure 6. Comparison of BBDR model predicted free T4 (fT4) changes as a function of
1156 perchlorate dose with data from Steinmaus et al. (2016). Reproduced from USEPA (2017).
1157 Blue boxes and diamonds represent the BBDR model predictions for median (170 µg/d) and
1158 low (90 µg/d) iodine intake populations (GW 13-16); red +'s represent the central estimate
1159 from the analysis of the Steinmaus et al. (2016) study and the red x's represent the upper
1160 and lower confidence limits for that estimate.

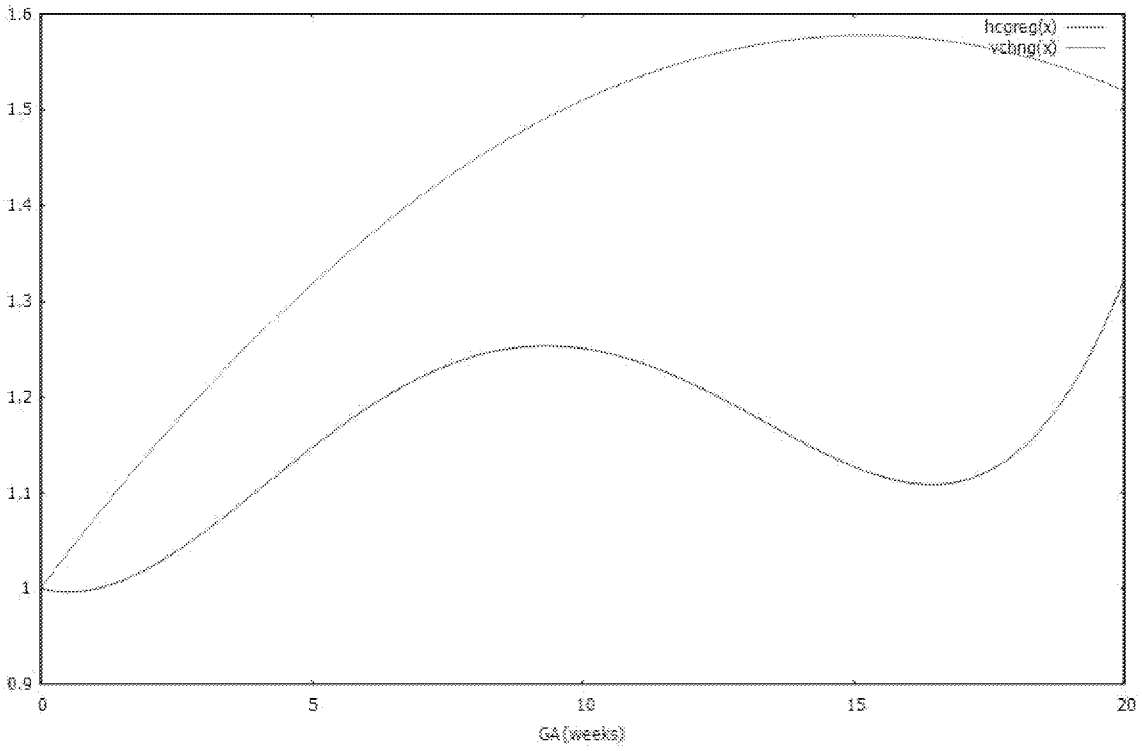
1161 Figure 7. Comparison of PoDs calculated using the USEPA (2017) BBDR model-based PoDs
1162 (blue and green bars) with the USEPA (2005) RfD (red bar).

1163









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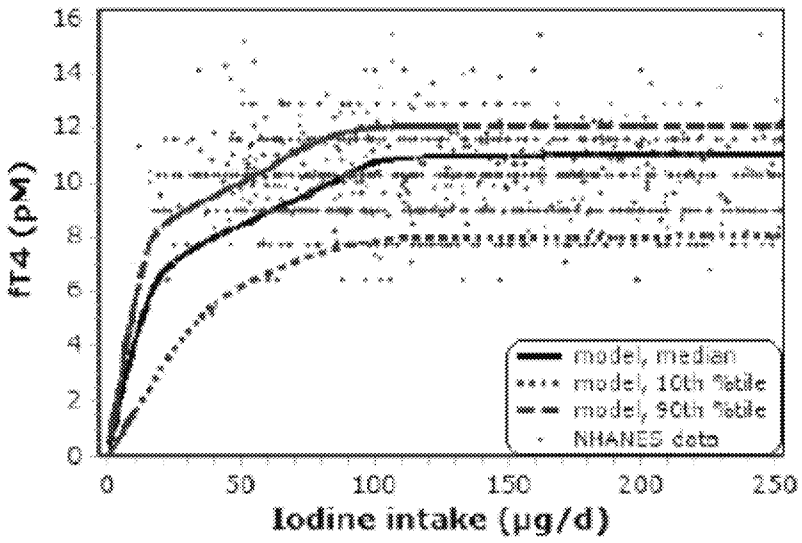

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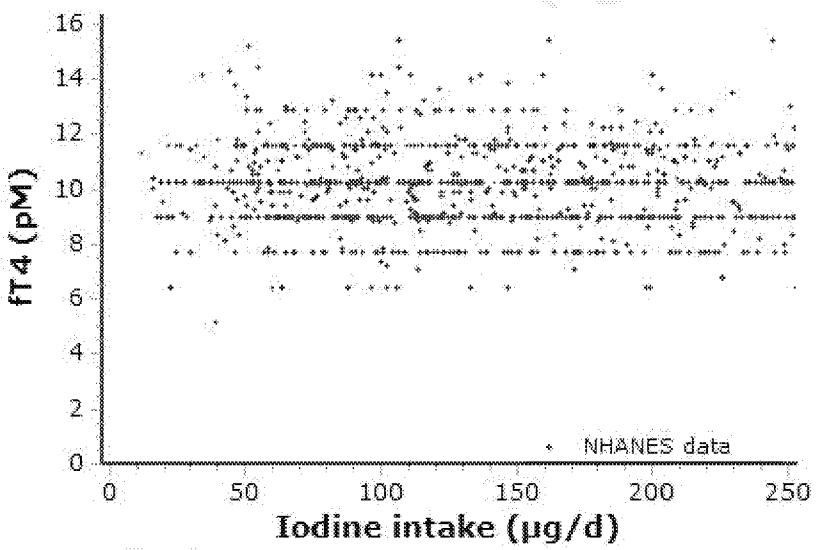

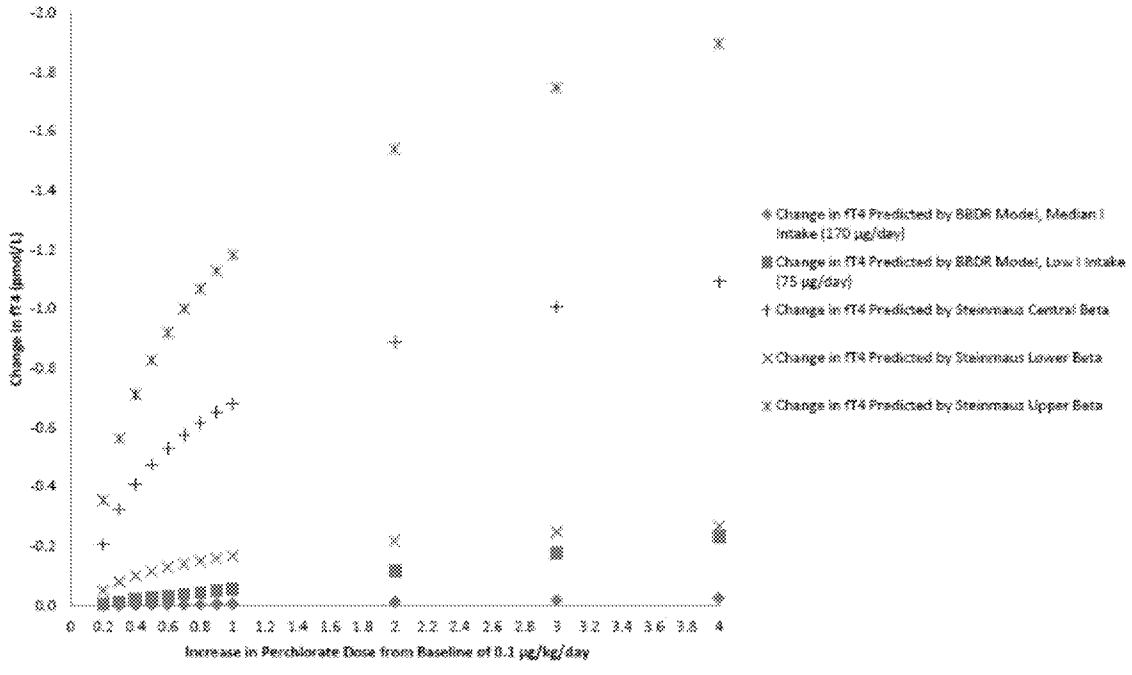

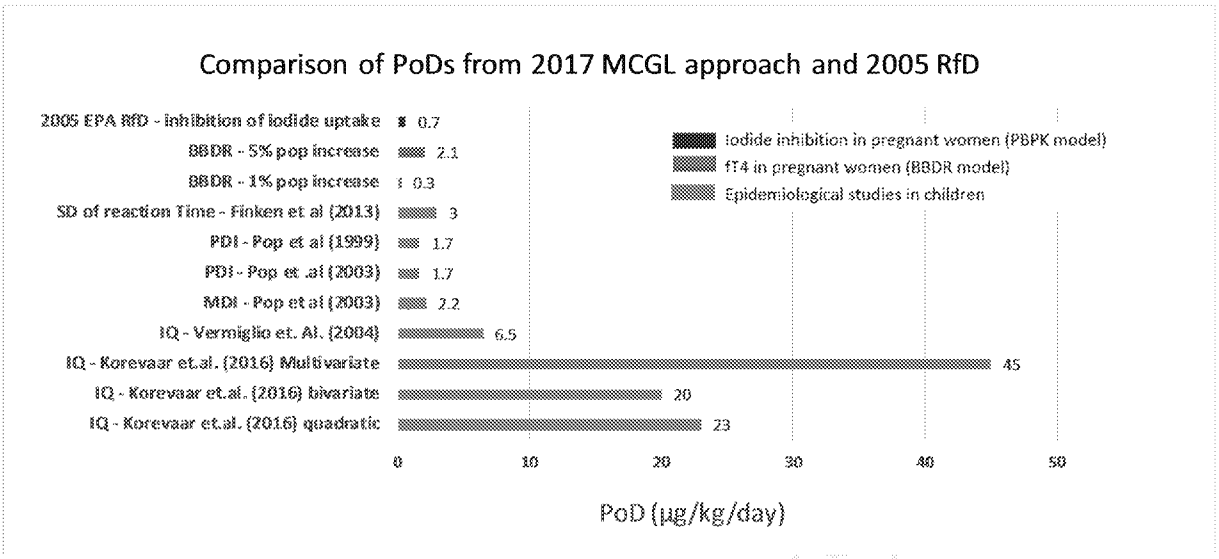

Highlights (maximum 125 characters, including spaces)

- The USEPA (2017) BBDR model plausibly describes perchlorate effects on thyroid hormone regulation during early pregnancy.
- The model is a valuable tool for investigating the effects of perchlorate on thyroid function during early gestation.
- BBDR modeling results indicate that the current USEPA RfD, based on adult effects, is also protective for fetal effects.
- However, current model uncertainties dictate against its use to replace the existing RfD for perchlorate.

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 141 and 142

[EPA-HQ-OW-2018-0780, EPA–HQ–OW–2008–0692, EPA–HQ–OW– 2009–0297; FRL-XXXX-XX-OW]

RIN 2040-AF28

Drinking Water: Notice of Final Action on Perchlorate

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final Action.

SUMMARY: The Environmental Protection Agency (EPA) is announcing its withdrawal of the 2011 determination to regulate perchlorate in accordance with the Safe Drinking Water Act (SDWA). On February 11, 2011, the EPA published a *Federal Register* notice in which the Agency determined that perchlorate met the SDWA's criteria for regulating a contaminant. On June 26, 2019, the EPA published a proposed national primary drinking water regulation (NPDWR) for perchlorate and requested public comments on multiple alternative regulatory actions, including the alternative of withdrawing the 2011 regulatory determination for perchlorate. The EPA received approximately 1,500 comments on the proposed rule. The EPA has considered these public comments and based on the best available information the Agency is

withdrawing the 2011 regulatory determination and is making a final determination to not regulate perchlorate. The EPA has determined that perchlorate does not occur with a frequency and at levels of public health concern, and that regulation of perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems.

DATES: For purposes of judicial review, the regulatory determination in this document is issued as of *[insert date of publication in the* Federal Register*]*.

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460; telephone number: (202) 564-1735; email address: hernandez.samuel@epa.gov.

SUPPLEMENTARY INFORMATION: This notice is organized as follows:

I. General Information

A. Does This Action Apply to Me?

This action will not impose any requirements on anyone. Instead, this action notifies interested parties of the EPA's withdrawal of the 2011 regulatory determination for perchlorate and the final regulatory determination to not regulate perchlorate. This notice also provides a

summary of the major comments received on the June 26, 2019 (84 FR 30524) proposed NPDWR for perchlorate.

B. How can I get Copies of this Document and other Related Information?

The EPA has established a docket for this action under Docket ID No. EPA–HQ–OW–2018–0780. Publicly available docket materials are available electronically at [HYPERLINK "http://www.regulations.gov/docket?D=EPA-HQ-OW-2018-0780"].

II. Background

A. What is Perchlorate?

Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms (ClO_4-), which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks. Perchlorate can also result from the degradation of hypochlorite solutions used for water disinfection. The degradation into perchlorate occurs when hypochlorite solutions are improperly stored and handled. For the general population, most perchlorate exposure is through the ingestion of contaminated food or drinking water. At certain levels, perchlorate can prevent the thyroid gland from getting enough iodine, which can affect thyroid hormone

production. For pregnant women with low iodine levels, sufficient changes in thyroid hormone levels may cause changes in the child's brain development. For infants, changes to thyroid hormone function can also impact brain development.

B. What is the purpose of this action?

The purpose of this action is to publish the EPA's notice to withdraw the 2011 regulatory determination and issue a final determination to not regulate perchlorate in drinking water. This notice presents the EPA's basis for this withdrawal and final regulatory determination, and the EPA's response to key issues raised by commenters in response to the June 26, 2019 (84 FR 30524) proposed rule (referred to hereinafter as "the 2019 proposal").

C. What is the EPA's statutory authority for this action?

The SDWA sets forth three criteria that must be met for the EPA to issue a maximum contaminant level goal (MCLG) and promulgate a national primary drinking water regulation (NPDWR). Specifically, the Administrator must determine that (1) "the contaminant may have an adverse effect on the health of persons"; (2) "the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern"; and (3) "in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems" (SDWA 1412(b)(1)(A)).

The EPA has determined, based on data and analysis since the issuance of the 2011 regulatory determination, that perchlorate does not in fact meet the statutorily-prescribed criteria

for regulation. As described in Sections III & VI of the 2019 proposal, the data and analysis in the record indicate that perchlorate does not occur in public water systems with a frequency and at levels of public health concern. Specifically, the peer-reviewed health effects analysis indicates that the concentration of perchlorate representing the levels of public health concern (i.e., the proposed MCLG levels, 18-90 µg/L) is higher than the concentration considered in issuance of the 2011 regulatory determination (1-47 µg/L) (USEPA, 2019a). In addition, based on an evaluation of the nationally representative UCMR 1 systems, the updated occurrence analysis shows that the frequency of occurrence of perchlorate in public water systems at levels exceeding any of the alternative proposed MCLGs is significantly lower (0.38% - 0.02%) than the frequency considered in the analysis for the 2011 regulatory determination (4% - 0.39%) (USEPA, 2019b). The EPA estimates that, even at the most stringent regulatory level considered in the 2019 proposal (18 µg/L), not more than 15 systems (0.03% of all water systems in the U.S.) would need to take action to reduce levels of perchlorate. Based on this information, the EPA determines that perchlorate does not occur in public water systems "with a frequency…of public health concern" and thus does not meet the second criterion of the three required for regulation under the SDWA. In addition, while the third criterion is "in the sole judgement of the Administrator," the low occurrence provides ample support for the EPA's conclusion that the regulation of perchlorate does not present a "meaningful opportunity for health risk reduction for persons served by public water systems," within the meaning of 1412(b)(1)(A)(iii). Accordingly,

because perchlorate no longer meets the statutory criteria for regulation, the EPA does not have the authority to issue a MCLG or promulgate a NPDWR for perchlorate.

The EPA's decision to withdraw the regulatory determination is supported by the legislative history underlying the 1996 amendments to the SDWA, which repealed the statutory requirement for the EPA to regulate an additional 25 contaminants every 3 years and replaced it with the current requirement for the EPA to determine whether regulation is warranted for five contaminants every five years. In describing the need for such amendment, the legislative history points to the view expressed at the Committee Hearing that "the current law is a one-size-fits-all program. It forces our water quality experts to spend scarce resources searching for dangers that often do not exist rather than identifying and removing real health risks from our drinking water" (S. Rep. 104-169 (1995) at 12). This amendment reflected Congress' clear intent that the EPA prioritize actual health risks in determining whether to regulate any particular contaminant. *See id* at 12 (noting that the amendment "repeals the requirement that the EPA regulate an additional 25 contaminants every 3 years replacing it with a new selection process that gives the EPA the discretion to identify contaminants that warrant regulation in the future").

The EPA's decision to withdraw the regulatory determination is also consistent with Congress' direction to prioritize the SDWA decisions based on the best available public health information. *See* 1412(b)(1)(B)(ii)(II) (findings supporting a determination to regulate "shall be based on the best available public health information"); 1412(b)(2)(A) (requiring that the EPA use "the best available, peer-reviewed science and supporting studies…" in carrying out any

actions under this section). Although the EPA determined in 2011 that perchlorate met the criteria for regulation, new data and analysis developed by the Agency as part of the 2019 proposal demonstrate that the occurrence and health effects information used as the basis for the 2011 determination no longer constitute "best available information," are no longer accurate and no longer support the Agency's prioritization of perchlorate for regulation. Accordingly, not only is EPA not authorized to issue a MCLG or promulgate a NPDWR for perchlorate, but it would not be in the public interest to do so.

The EPA recognizes that the Act does not include a provision explicitly authorizing withdrawal of a regulatory determination. However, such authority is inherent in the authority to issue a regulatory determination under 1412(b)(1)(B)(ii)(II), particularly given the requirement that such determination be based on the "best available public health information," as discussed above. Accordingly, the EPA must have the inherent authority to withdraw a regulatory determination if the underlying information changes between regulatory determination and promulgation. In light of its concern that the EPA focus new contaminant regulations on priority health concerns, Congress could not have intended that the EPA's regulatory decision-making be hamstrung by older data when newer, more accurate scientific and public health data are available, especially when those data demonstrate that regulation of a new contaminant would not present a meaningful opportunity for health risk reduction.

Moreover, the EPA notes that the statute specifically provides that a decision to not regulate a contaminant is a final Agency action subject to judicial review. SDWA, section

1412(b)(1)(B)(ii)(IV). Congress could have – but did not – specify the same with respect to determinations to regulate. Congress also did not explicitly prohibit the EPA from withdrawing or modifying a regulatory determination. Congress' silence with respect to determinations to regulate suggests that Congress intended that such a determination is not itself a final agency action, but rather a preliminary step in a decision-making process culminating in a NPDWR and thus subject to reconsideration based on new data and analysis considered during the 36 month promulgation process specified in the statute. Accordingly, reconsideration of this preliminary finding – and withdrawal of the determination based on subsequent analysis mandated for NPDWR development – is fully consistent with the statutory decision-making framework.

D. Statutory Framework and Perchlorate Regulatory History

Section 1412(b)(1)(B)(i) of the SDWA requires the EPA to publish every five years a Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to federal drinking water regulations. The EPA uses the CCL to identify priority contaminants for regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998 (63 FR 10274), 2005 (70 FR 9071), and 2009 (74 FR 51850).

The EPA collects data on the CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in public water systems. SDWA, section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after consideration of public

comment, issue a determination of whether or not to regulate at least five contaminants on each CCL. For any contaminant that the EPA determines meets the SDWA criteria for regulation, under SDWA, section 1412(b)(1)(E), the EPA must propose a NPDWR within two years and promulgate a final regulation within 18 months of the proposal (which may be extended by 9 additional months).

As part of its responsibilities under the SDWA, the EPA implements section 1445(a)(2), "Monitoring Program for Unregulated Contaminants." This section requires that once every five years, the EPA issue a list of no more than 30 unregulated contaminants to be monitored by public water systems. This monitoring is implemented through the Unregulated Contaminant Monitoring Rule (UCMR), which collects data from community water systems and non-transient, non-community water systems. The first four UCMRs collected data from a census of large water systems (serving more than 10,000 people) and from a statistically representative sample of small water systems. On September 17, 1999, the EPA published its first UCMR (64 FR 50556), which required all large systems and a representative sample of small systems to monitor for perchlorate and 25 other contaminants (USEPA, 1999). Water system monitoring data for perchlorate was collected from 2001 to 2005.

The EPA and other federal agencies asked the National Research Council (NRC) to evaluate the health implications of perchlorate ingestion. In its 2005 report, the NRC concluded

that perchlorate exposure inhibits the transport of iodide[1] into the thyroid by a protein molecule known as the sodium/iodide symporter (NIS), which may lead to decreases in two thyroid hormones, thyroxine (T3) and triiodothyronine (T4), and increases in thyroid-stimulating hormone (TSH) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, the NRC concluded that the most sensitive population to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" (p. 178). The EPA established a reference dose (RfD) consistent with the NRC's recommended RfD of 0.7 μg/kg/day for perchlorate. The reference dose is an estimate of a human's daily exposure to perchlorate that is likely to be without an

[1] For the purposes of this notice, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

appreciable risk of adverse effects. This RfD was based on a study [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3u94lt6me","properties":{"formattedCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","plainCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","noteIndex":0},"citationItems":[{"id":387,"uris":["http://zotero.org/groups/945096/items/6AKUNIX6"],"uri":["http://zotero.org/groups/945096/items/6AKUNIX6"],"itemData":{"id":387,"type":"article-journal","title":"Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans","container-title":"Environmental Health Perspectives","page":"927","volume":"110","issue":"9","author":[{"family":"Greer","given":"Monte A."},{"family":"Goodman","given":"Gay"},{"family":"Pleus","given":"Richard C."},{"family":"Greer","given":"Susan E."}],"issued":{"date-parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0oHz805e","properties":{"formattedCitation":"(USEPA, 2005b)","plainCitation":"(USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":980,"uris":["http://zotero.org/groups/945096/items/LHANJBR6"],"uri":["http://zotero.org/groups/945096/items/LHANJBR6"],"itemData":{"id":980,"type":"article","title":"Integrated Risk Information System (IRIS) Chemical Assessment

Summary: Perchlorate (ClO4-) and Perchlorate Salts","publisher":"USEPA National Center for Environmental Assessment","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In October 2008, the EPA published a preliminary regulatory determination to not regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA found that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 μg/L based on the RfD of 0.7 μg/kg/day and body weight and exposure information for pregnant women in making this conclusion [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"FZ6WMtAv","properties":{"formattedCitation":"(USEPA, 2008a)","plainCitation":"(USEPA, 2008a)","noteIndex":0},"citationItems":[{"id":934,"uris":["http://zotero.org/groups/945096/items/HBX88QM9"],"uri":["http://zotero.org/groups/945096/items/HBX88QM9"],"itemData":{"id":934,"type":"article-journal","title":"Drinking water: Preliminary regulatory determination on perchlorate","container-title":"Federal Register","volume":"73","issue":"198","abstract":"SUMMARY: This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water

Act (SDWA). The Agency has determined that a national primary drinking water regulation (NPDWR) for perchlorate would not present \"a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). EPA included perchlorate on the first and second CCLs that were published in the Federal Register on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the Federal Register on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with technical information that they may use in addressing local contamination.","ISSN":"ISSN 0097-6326 EISSN 2167-2520","shortTitle":"Federal Register","journalAbbreviation":"Fed. Reg.","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Using the UCMR 1 occurrence data, the EPA estimated that less than 1% of drinking water systems (serving approximately 1 million people) had perchlorate levels above the HRL of 15 µg/L. Based on this information the EPA found that

perchlorate did not occur at a frequency and at levels of public health concern. The EPA also determined there was not a meaningful opportunity for a NPDWR for perchlorate to reduce health risks.

In August 2009, the EPA published a supplemental request for comment with new analysis that derived potential alternative Health Reference Levels (HRLs) for 14 life stages, including infants and children. The analysis used the RfD of 0.7 µg/kg/day and life stage-specific bodyweight and exposure information, resulting in comparable perchlorate concentrations in drinking water, based on life stage, of between 1 µg/l to 47 µg/l (74 FR 41883; USEPA, 2009).

In February 11, 2011, the EPA published its determination to regulate perchlorate (76 FR 7762; USEPA, 2011) after careful consideration of public comments on the October 2008 and August 2009 notices. The EPA found at that time that perchlorate may have an adverse effect on the health of persons, it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA stated then that: "*Based on the data in Table 1 and the range of potential alternative HRLs, EPA has determined that perchlorate is known to occur or there is a substantial likelihood that it will occur with a frequency and at levels of public health concern.*"(USEPA, 2011, p. 7765). The EPA found that as many as 16 million people could potentially be exposed to perchlorate at levels of concern, up from 1 million people originally estimated in the 2008 notice.

As a result of the determination, and as required by SDWA, section 1412(b)(1)(E), the EPA initiated the process to develop a MCLG and a NPDWR for perchlorate.

In September 2012, the U.S. Chamber of Commerce (the Chamber) submitted to the EPA a Request for Correction under the Information Quality Act regarding the EPA's regulatory determination. In the request, the Chamber claimed that the UCMR 1 data used in the EPA's occurrence analysis did not comply with data quality guidelines and were not representative of current conditions. In response to this request, the EPA reassessed the data and removed certain source water samples that could be paired with appropriate follow-up samples located at the entry point to the distribution system. The EPA also updated the UCMR 1 data in the analysis for systems in California and Massachusetts, using state compliance data to reflect current occurrence conditions after state regulatory limits for perchlorate were implemented.

As required by section 1412(d) of the SDWA, as part of the NPDWR development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK) analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. In May 2013, the SAB recommended that the EPA:

- derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling based upon its mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;

- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition—to thyroid hormone changes—and finally to neurodevelopmental impacts; and
- ''Extend the [BBDR] model expeditiously to . . . provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages''(SAB for the U.S. EPA, 2013, p. 19).

To address the SAB recommendations, the EPA revised an existing PBPK/PD model that describes the dynamics of perchlorate, iodide, and thyroid hormones in a woman during the third trimester of pregnancy (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b). The EPA also created its own Biologically Based Dose Response (BBDR) models that included the additional sensitive life stages identified by the SAB, *i.e.,* breast- and bottle-fed neonates and infants (SAB for the U.S. EPA, 2013, p. 19).

To determine whether the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in January 2017 (External Peer Reviewers for USEPA, 2017). The EPA considered the recommendations from the 2017 peer review and made necessary model revisions to increase the scientific rigor of the model and the modeling results.

The EPA convened a second independent peer review panel in January 2018 to evaluate the revisions to the BBDR model. The EPA also presented several approaches to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects using evidence from the epidemiological literature (External Peer Review for U.S. EPA, 2018).

In response to a lawsuit brought to enforce the deadlines in SDWA, section 1412(b)(1)(E), on October 18, 2016, the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to sign for publication a proposal for a MCLG and NPDWR for perchlorate in drinking water no later than October 31, 2018, and to sign for publication a final MCLG and NPDWR for perchlorate in drinking water no later than December 19, 2019. The deadline for the EPA to propose a MCLG and NPDWR for perchlorate in drinking water was later extended to May 28, 2019, and the date for signature of a final MCLG and NPDWR was extended to be no later than June 19, 2020. The consent decree is available in the docket for this action.

In compliance with the deadline established in the consent decree, on May 23, 2019, the EPA Administrator signed a proposed rulemaking notice seeking public comment on a range of options regarding the regulation of perchlorate in public drinking water systems. The proposed rulemaking notice was published in the *Federal Register* on June 26, 2019. 84 Fed. Reg. 30524. The EPA proposed a NPDWR for perchlorate with an MCL and MCLG of 56 μg/L. The proposed MCLG of 56 μg/L was based on avoiding a 2 point IQ decrement associated with

exposure to perchlorate in drinking water during the most sensitive life stage (the fetus) within a specific segment of the population (iodine deficient pregnant women).

The EPA also requested comment on two alternative MCL/MCLG values of 18 µg/L and 90 µg/L. These alternatives were based upon avoiding 1 point and 3 point IQ decrements respectively, associated with perchlorate exposure. Additionally, the EPA requested comment on whether the 2011 regulatory determination should be withdrawn, based on new information including updated occurrence data on perchlorate in drinking water and new analysis of the concentration of perchlorate in drinking water that represents a level of health concern.

III. Withdrawal of the 2011 Regulatory Determination and Final Determination to Not Regulate Perchlorate

In determining whether to regulate a particular contaminant, the EPA must follow the criteria mandated by the 1996 SDWA Amendments. Specifically, in order to issue a MCLG and NPDWR for perchlorate, the EPA must determine that perchlorate "may have an adverse effect on the health of persons," that perchlorate occurs at "a frequency and at levels of public health concern" in public water systems, and that regulation of perchlorate in drinking water systems "presents a meaningful opportunity for health risk reduction for persons served by public water systems." SDWA, section 1412(b)(1)(A). In preparing the 2019 proposal for perchlorate, the EPA updated and improved information on the levels of public health concern and the frequency and levels of perchlorate in public water systems. The following is the EPA's reassessment of the

regulatory determination criteria applied to the best available health science and occurrence data for perchlorate.

A. May perchlorate have an adverse effect on the health of persons?

Yes, perchlorate may have adverse health effects. The perchlorate anion is biologically significant specifically with respect to the functioning of the thyroid gland. Perchlorate can interfere with the normal functioning of the thyroid gland by inhibiting the transport of iodide into the thyroid, resulting in a deficiency of iodide in the thyroid. Perchlorate inhibits (or blocks) iodide transport into the thyroid by chemically competing with iodide, which has a similar shape and electric charge. The transfer of iodide from the blood into the thyroid is an essential step in the synthesis of thyroid hormones. Thyroid hormones play an important role in the regulation of metabolic processes throughout the body and are also critical to developing fetuses and infants, especially for brain development. Because the developing fetus depends on an adequate supply of maternal thyroid hormones for its central nervous system development during the first and second trimester of pregnancy, iodide uptake inhibition from perchlorate exposure has been identified as a concern in connection with increasing risk of neurodevelopmental impairment in fetuses of pregnant women with low dietary iodine. Poor iodide uptake and subsequent impairment of the thyroid function in pregnant and lactating women have been linked to delayed development and decreased learning capability in their infants and children (NRC, 2005). Therefore, the EPA continues to find that perchlorate may have an adverse effect on the health of persons.

B. Is perchlorate known to occur or is there a substantial likelihood that perchlorate will occur in public water systems with a frequency and at levels of public health concern?

The EPA has determined that perchlorate does not occur with a frequency and at levels of public health concern in public water systems. The EPA has made this determination by comparing the best available data on the occurrence of perchlorate in public water systems to potential MCLGs for perchlorate.

In past regulatory determinations, the EPA has identified HRLs as benchmarks against which the EPA compares the concentration of a contaminant found in public water systems to determine if it occurs at levels of public health concern. For the 2011 regulatory determination the EPA identified potential HRLs values ranging from 1 to 47 μg/L for 14 different life stages. These HRLs were not final decisions about the level of perchlorate in drinking water that is without adverse effects. For the 2019 proposal, the EPA derived three potential MCLGs for perchlorate of 18, 56, and 90 μg/L for the most sensitive life stage using the best available peer reviewed science in accordance with the SDWA. After considering public comment, the EPA used these potential MCLGs as the levels of public health concern in assessing the frequency of occurrence of perchlorate in this regulatory determination. These MCLGs were set at levels to avoid IQ decrements of 1, 2, and 3 points respectively in the most sensitive life stage, the children of hypothyroxinemic women with low iodine intake. The EPA proposed an MCLG of 56 μg/L and alternative MCLG values of 18 and 90 μg/L.

The rationale used in deriving the numerical values is presented in greater detail in the EPA's technical support document titled "Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" (USEPA, 2019b).

The EPA compared these potential MCLG values to the updated perchlorate UCMR 1 occurrence data set. A comprehensive description of the perchlorate occurrence data is presented in Section VI of the 2019 proposal. It is also available in the "Perchlorate Occurrence and Monitoring Report" (USEPA, 2019a).

The occurrence data for perchlorate were collected from 3,865 PWSs between 2001 and 2005 under the UCMR 1. In the 2019 proposal, the EPA modified the UCMR 1 data set in response to concerns raised by stakeholders regarding the data quality and to represent current conditions in California and Massachusetts, which have enacted perchlorate regulations since the UCMR 1 data were collected. Massachusetts promulgated a drinking water standard for perchlorate of 2 μg/L in 2006 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8DPpSrv3","properties":{"formattedCitation":"(MassDEP, 2006)","plainCitation":"(MassDEP, 2006)","noteIndex":0},"citationItems":[{"id":151,"uris":["http://zotero.org/groups/945096/items/9893MBZH"],"uri":["http://zotero.org/groups/945096/items/9893MBZH"],"itemData":{"id":151,"type":"personal_communication","title":"Letter to Public Water Suppliers concerning new perchlorate regulations","URL":"https://www.mass.gov/lists/perchlorate-background-information-and-standards#perchlorate---final-standards-

","author":[{"literal":"MassDEP"}],"issued":{"date-parts":[["2006"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and California promulgated a drinking water standard of 6 µg/L in 2007 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cfr6HNhg","properties":{"formattedCitation":"(California Department of Public Health, 2007)","plainCitation":"(California Department of Public Health, 2007)","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/groups/945096/items/RA45NKLQ"],"uri":["http://zotero.org/groups/945096/items/RA45NKLQ"],"itemData":{"id":150,"type":"personal_communication","title":"State Adoption of a Perchlorate Standard","URL":"https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/perchlorate/AdoptionMemotoWaterSystems-10-2007.pdf","author":[{"literal":"California Department of Public Health"}],"issued":{"date-parts":[["2007"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Systems in these states are now required to keep perchlorate levels in drinking water below their state limits. As discussed below, the EPA finds that perchlorate levels in drinking water and sources of drinking water have decreased since the UCMR 1 data collection. The main factors contributing to the decrease in perchlorate levels are the promulgation of drinking water regulations for perchlorate in California and Massachusetts and the ongoing remediation efforts in the state of Nevada to address perchlorate contamination in groundwater adjacent to the lower Colorado River upstream of Lake Mead.

To update the occurrence data for systems sampled during UCMR 1 from California and Massachusetts, the EPA identified all systems and corresponding entry points which had reported perchlorate detections in UCMR 1. Once the systems and entry points with detections were appropriately identified, the EPA then used a combination of available data from Consumer Confidence Reports (CCRs) and perchlorate compliance monitoring data from California (https://sdwis.waterboards.ca.gov/PDWW/) and Massachusetts (https://www.mass.gov/service-details/public-water-supplier-document-search) to match current compliance monitoring data (where available) to the corresponding water systems and entry points sampled during UCMR 1.

The EPA has determined that the UCMR 1 data with these updates are the best available data collected in accordance with accepted methods regarding the frequency and level of perchlorate nationally. The UCMR 1 data are from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems that provides the best available, national assessment of perchlorate occurrence in drinking water.

The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the potential MCLG thresholds. The maximum measurements indicate highest perchlorate levels reported in at least one quarterly sample from surface water systems and at least one semi-annual sample from ground water systems.

Table 1: Perchlorate Occurrence and Exposure (Updated UCMR 1 Data Set)

Threshold Concentration (µg/L)	Entry Points with Detections above Threshold	Water Systems with Detections above Threshold	Percent of U.S. Water Systems with Detections above Threshold	Population Served

18 µg/L	17	15	0.03 %	620,560
56 µg/L	2	2	0.004 %	32,432
90 µg/L	1	1	0.002 %	25,972

Table 1 presents the number and percentage of water systems that reported perchlorate at levels exceeding the three proposed MCLG threshold concentrations. In summary, the updated perchlorate occurrence information suggests that at an MCLG of 18 µg/L, there would be 15 systems (0.03% of all water systems in the U.S.) that would exceed the threshold, at an MCLG of 56 µg/L, two systems (0.004% of all water systems in the U.S.) would exceed the threshold, and finally one system would exceed the MCLG threshold of 90 µg/L. Based on the analysis of drinking water occurrence presented in the 2019 proposal and the data summarized in Table 1 and the range of potential MCLGs, the EPA concludes that perchlorate does not occur with a frequency and at levels of public health concern in public water systems.

While the EPA has made its conclusion that perchlorate does not occur at a frequency and at levels of public health concern in public water systems based on the updated UCMR 1 data, the EPA also sought to find additional information about the perchlorate levels at the 15 water systems that had at least one reported result greater than 18 µg/L in the updated UCMR 1 data. The EPA found that perchlorate levels have been reduced at many of these water systems. Although these water systems were not required to take actions to reduce perchlorate in drinking

water, many had conducted additional monitoring for perchlorate and found decreased levels or had taken mitigation efforts to address perchlorate, confirming the EPA's conclusion described above. The status of each of these systems is described in Table 2 below.

Table 2: Update on Systems with Perchlorate levels above 18 µg/L in the UCMR 1

State	System Name	Range of UCMR 1 Results (µg/L)**	Update on Mitigation and Levels of Perchlorate++
Florida	Sebring Water	ND-70	The EPA contacted the Sebring system in January 2020. Operations personnel indicated that no follow-up/updated monitoring data for perchlorate are available.
Florida	Manatee County Utilities Dept	ND-30	Researchers contacted the system to identify the source of perchlorate. System personnel attributed the sole perchlorate detection under UCMR 1 to analytical error. System personnel indicated that three other quarterly samples collected under UCMR 1 as well as other subsequent perchlorate sampling efforts were non-detect. Source: AWWA (2008)
Georgia	Oconee Co.-Watkinsville	38 (single sample)	Researchers contacted the system and found that a perchlorate contaminated well was removed from service in 2003. The system indicates that perchlorate is no longer detected. Source: Luis et al. (2019)
Louisiana	St. Charles Water District 1 East Bank	ND-24	The EPA was not able to identify updated data on perchlorate levels for this system.
Maryland	City of Aberdeen	ND-19	The system's 2018 Consumer Confidence Report (CCR) indicates that perchlorate was not detected. According to the Maryland Department of Environment, perchlorate was not detected in this system in 2019. In addition, researchers contacted the system and found that there has been no detection of

State	System Name	Range of UCMR 1 Results (µg/L)**	Update on Mitigation and Levels of Perchlorate++
			perchlorate since treatment was installed in 2009. Source: Luis et al. (2019)
Maryland	Chapel Hill - Aberdeen Proving Grounds	ND-20	The EPA contacted the Chapel Hill System in January 2020. Water system personnel indicate that the Chapel Hill WTP was taken off-line and was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicate that monitoring was conducted in November 2019 and perchlorate was not detected in either the source well water or the finished water. In addition, according to the Maryland Department of Environment, perchlorate was not detected in this system in 2019.
Mississippi	Hilldale Water District	ND-20	The EPA contacted the Hilldale System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate are available.
New Mexico	Deming Municipal Water System	15-20	Data from the EPA's SDWIS/FED database indicates that the entry point that reported detections in UCMR 1 (Well #3) is now inactive (i.e., the contaminated source is no longer in use).
Nevada	City of Henderson	6-23	Researchers report that the perchlorate levels described in the system's CCR ranged from non-detect to 9.7 µg/L. Source AWWA (2008).
Ohio	Fairfield City PWS	6-27	The EPA contacted the Fairfield City System in January 2020. Water system personnel indicated that follow-up monitoring was conducted after UCMR 1, between 2002 and 2004. The Ohio EPA provided copies of the follow-up monitoring results which

State	System Name	Range of UCMR 1 Results (µg/L)**	Update on Mitigation and Levels of Perchlorate++
			indicate that results at the entry point ranged from non-detect to 13 µg/L.
Ohio	Hecla Water Association-Plant PWS	ND-32	The EPA contacted the Hecla Water Association System in January 2020. Water system personnel indicated that that no follow-up/updated monitoring data for perchlorate are available.
Oklahoma	Enid	ND-30	The EPA reviewed Oklahoma's monitoring data and did not find any monitoring results reported for perchlorate.
Pennsylvania	Meadville Area Water Authority	ND-33	The EPA contacted the Meadville System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate are available.
Puerto Rico	Utuado Urbano	ND-420	The EPA contacted the Puerto Rico Aqueduct and Sewer Authority (PRASA) in January 2019. PRASA personnel indicated that no updated monitoring data for perchlorate are available. *NOTE: The PRASA personnel stated that the Utuado water system was significantly impacted by hurricane Maria and monitoring records from years prior to 2017 were lost.*
Texas	City of Levelland	ND-32	Researchers found that a water storage tank was the source of perchlorate contamination, the wells feeding the tank were tested by the state and perchlorate was not detected. The water tank was shut off from service. Source: Luis et al. (2019).

** - Values have been rounded. ND describes a sampling event where perchlorate was not detected at or above the UCMR 1 minimum reporting level of 4 µg/L. UCMR 1 results collected between 2001 and 2005.

++ - To obtain updated data and/or information regarding perchlorate levels, the EPA reviewed Consumer Confidence Reports and other publicly available data, as well as published studies. In addition, the EPA contacted some water systems for information about current perchlorate levels. (USEPA, 2020b)

C. Is there a meaningful opportunity for the reduction of health risks from perchlorate for persons served by public water systems?

The EPA's analysis presented in the 2019 proposal demonstrates that a NPDWR for perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems. As discussed above, the EPA found that perchlorate occurs with very low frequency at levels of public health concern. Based on updated UCMR 1 occurrence information, there were 15 water systems (0.03% of all water systems in the U.S.) that detected perchlorate in drinking water above the lowest proposed alternative MCLG of 18 µg/L and only 1 system had a detection above the proposed alternative MCLG of 90 µg/L. Specifically, Table 1 presents the population served by PWSs that were monitored under UCMR 1 for which the highest reported perchlorate concentration was greater than the identified thresholds. The EPA estimates[2] that the number of people who may be potentially consuming water containing perchlorate at levels that could exceed the levels of concern for perchlorate could range between 26,000 and 620,000. The small number of water systems with perchlorate levels greater than identified thresholds and the corresponding small population served provides ample support for the EPA's conclusion that the regulation of perchlorate does not present a "meaningful

[2] The values shown in Table 1 are based on the revised UCMR 1 data. The EPA also applied statistical sampling weights to the small systems results to extrapolate to national results. There was one small system included in the statistical sample stratum which had a perchlorate measurement exceeding 18 µg/L. Accordingly, the EPA estimates that approximately 41,000 small system customers may be exposed to perchlorate greater than 18 µg/L.

opportunity for health risk reduction for persons served by public water systems," within the meaning of SDWA, section 1412(b)(1)(A)(iii).

The EPA also considered the findings of the Health Risk Reduction and Cost Analysis (HRRCA, USEPA 2019c) as additional information supporting withdrawal of the regulatory determination. The HRRCA for perchlorate (which was presented in the 2019 proposal) provides a unique set of economic data indicators that are not available for regulatory determinations because the HRRCA is required for a proposed NPDWR under SDWA Section 1412(b)(3)(C), but is not required to support a regulatory determination. Accordingly, because the EPA initially determined that perchlorate met the criteria for regulation and began the regulatory analysis process, the HRRCA was available with respect to perchlorate, and the Agency considered this comprehensive economic analysis in informing its decision to withdraw the regulatory determination.

Specifically, the HRRCA provides a description of the potential benefits and costs of a drinking water regulation for perchlorate. For all potential regulatory levels considered for perchlorate (18, 56, and 90 μg/L) the total costs associated with establishing a regulation were substantially higher than the potential range of benefits. The infrequent occurrence of perchlorate at levels of health concern imposes high monitoring and administrative cost burdens on public water systems and the states, while having little impact on health risk reductions and the associated low estimates of benefits.

Based on a comparison of costs and benefits estimated at the three potential regulatory levels, the EPA determined in the 2019 proposal that the benefits of establishing a drinking water regulation for perchlorate do not justify the potential costs.

A drinking water regulation for perchlorate would impose significant burden on states and water systems, mainly associated with requirements for monitoring but which would result in very few systems having to take action to reduce perchlorate levels. It is of paramount importance that water systems (particularly medium, small and economically distressed systems) focus their limited resources on actions that ensure compliance with existing NPDWRs and maintain their technical, managerial, and financial capacity to improve system operations and the quality of water being provided to their customers rather than spending resources monitoring for contaminants that are unlikely to occur.

D. What is the EPA's final regulatory determination on perchlorate?

Based on the EPA's analysis of the best available public health information, and after careful review and consideration of public comments on the June 2019 proposal, the Agency is withdrawing its 2011 determination and is making a final determination to not regulate perchlorate. Accordingly, the EPA will not issue a NPDWR for perchlorate at this time. While the EPA has found that perchlorate may have an adverse effect on human health, based on the analysis presented in this notice and supporting record, the EPA has determined that perchlorate does not occur in public water systems with a frequency and at levels of public health concern and that regulation of perchlorate does not present a meaningful opportunity to reduce health risks for persons served by public water systems. This conclusion is based on the best available

peer reviewed science and data collected in accordance with accepted methods on perchlorate health effects and occurrence.

IV. Summary of Key Public Comments on Perchlorate

The EPA received approximately 1,500 comments from individuals or organizations on the June 2019 proposal. This section briefly discusses the key technical issues raised by commenters and the EPA's response. Comments are also addressed in the ''Comment Response Document for the Final Regulatory Action for Perchlorate'' (USEPA, 2020a) available at http://www.regulations.gov (Docket ID No. EPA–HQ–OW–2018–0780).

A. SDWA Statutory Requirements and the EPA's Authority

The EPA received comments stating the Agency should promulgate an MCLG and MCL for perchlorate and comments stating the Agency should not promulgate a regulation. After considering these comments the EPA has re-evaluated perchlorate in accordance with SDWA, section 1412(b)(1)(A), which requires that the Agency promulgate a NPDWR if (i) the contaminant may have an adverse effect on the health of persons; (ii) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and (iii) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The EPA has determined, based upon the best available peer reviewed science and data collected in accordance with accepted methods, that perchlorate does not occur at a

frequency and at levels of public health concern, and that regulation of perchlorate does not present a meaningful opportunity for health risk reduction. Because perchlorate does not meet the statutory criteria for regulation, the EPA lacks the authority to issue a MCLG or NPDWR for perchlorate, and is therefore withdrawing its 2011 regulatory determination and issuing this final determination to not regulate perchlorate. For more information regarding EPA's statutory authority to withdraw its regulatory determination, see Section II.C above.

B. Health Effects Assessment

Health Effects/MCLG Derivation

The EPA received comments indicating that the Agency should utilize different approaches to derive the MCLG for perchlorate including approaches that some states used to develop their perchlorate advisory levels or drinking water standards. The EPA considered a number of alternative approaches to develop the MCLG for perchlorate and in accordance with SDWA, section 1412(e), the Agency sought recommendations from the Science Advisory Board. The EPA derived the proposed MCLG for perchlorate based on the approach recommended by the Science Advisory Board (SAB) (SAB for the U.S. EPA, 2013). The SAB recommended that *"the EPA derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling based upon its mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters."* The EPA has implemented these recommendations and has obtained two independent peer reviews of the analysis. These peer

reviewers stated that: "*Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments below, the current models are fit-for-purpose to determine an MCLG*" (External Peer Reviewers for USEPA, 2018, p. 2).

The EPA received comments indicating the most sensitive life stages were not selected and/or considered in the Agency's approach. The EPA disagrees. Gestational exposure to perchlorate during neurodevelopment is the most sensitive time period. The NRC concluded that the population most sensitive to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}]. In addition, there is clear evidence that disrupted maternal thyroid hormone levels during gestation can impact neurodevelopment later in life (Alexander et al., 2017; Costeira et al., 2011; Endendijk et al., 2017; Ghassabian, Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016; Morreale de Escobar, Obregón, & Escobar del Rey, 2004; Noten et al., 2015; Pop et al., 2003, 1999; SAB for the U.S. EPA, 2013; Thompson et al., 2018; van Mil et al., 2012; Wang et al., 2016; Zoeller & Rovet, 2004; Zoeller et al., 2007). The available data demonstrate that the fetus of the first trimester pregnant mother, when compared to other life-stages, experiences the greatest impact from the same dose of perchlorate, which is described in detail in Section 6 of the document "Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" (USEPA, 2019a). Some commenters suggested that the bottle-fed infant is a more sensitive life-stage. The EPA disagrees as described in the January 2017 Peer Review Report on the original Biologically Based Dose Response (BBDR) model, the bottle-fed infant's thyroid hormone levels were not impacted by doses of perchlorate up to 20 µg/day (External Peer Reviewers for USEPA, 2017). This lack of any impact is due primarily to the iodine in the formula, which offsets the impact of perchlorate on the thyroid.

The EPA received comments advocating for the use of the population-based approach evaluating the shift in the proportion of a population that would fall below a hypothyroxinemic cut point under a perchlorate exposure scenario. The EPA chose to

develop the MCLG using dose-response functions from the epidemiological literature to estimate neurodevelopmental impacts in the offspring of pregnant women exposed to perchlorate. The EPA selected this proposed approach because it is consistent with the SDWA's definition of a MCLG to avoid adverse health effects and because it is most consistent with the SAB recommendations. In addition, the fact that thyroid hormone levels vary by reference population and that there is not a defined value representing hypothyroxinemia makes the population-based approach less desirable than the approach selected (USEPA, 2018).

End Point Selection/Basis

The EPA received comments regarding the magnitude of an IQ change which should be used in deriving the MCLG. The EPA's proposed MCLG was based upon avoiding a 2% change in IQ in the most sensitive life stage and the EPA also requested comment on alternative options for the MCLG that would respectively avoid 1% or 3% change in IQ in the most sensitive life stage. Many comments stated that the EPA should at most consider a 1% IQ change. However, several commenters stated a 3% change is too small to have a meaningful impact and suggested the EPA consider a higher IQ percent change.

The EPA uses a variety of science policy approaches to select points of departure for developing regulatory values. For instance, in noncancer risk assessment the EPA often uses a percentage change in value. When assessing toxicological data, a 10 % extra risk (for discrete data), or a 1 standard deviation (i.e., 15 IQ points) change from the mean (for

continuous data) is often used (USEPA, 2012). A smaller response to inform a POD has been applied when using epidemiological literature because there is an inherently more direct relationship between the study results and the exposure context and health endpoint.

Given the difficulty in identifying a response below which no adverse impact occurs when considering a continuous outcome in the human population, the EPA looked to its Benchmark Dose Guidance (2012) for insight regarding a starting point. Specifically, ''[a] BMR of 1% has typically been used for quantal human data from epidemiology studies'' (p. 21, USEPA, 2012). For the specific context of setting an MCLG for perchlorate, the EPA evaluated the level of perchlorate in water associated with a 1% decrease, a 2% decrease, and a 3 percent decrease in the mean population IQ (i.e., 1, 2 and 3 IQ points).

In evaluating the frequency and level of occurrence of perchlorate in drinking water the EPA has found that perchlorate does not occur with frequency even at the lowest alternative MCLG of 18 µg/L which is based upon avoiding a 1% change in IQ in the most sensitive life stage.

The EPA received comments that the proposed MCLG did not incorporate an adequate margin of safety to comply with the SDWA. The EPA disagrees that it failed to use an adequate margin of safety. The EPA's assessment focused upon the most sensitive subset of the population, specifically offspring whose mothers had low (75 µg/day) iodine intake and were hypothyroxinemic (fT4 in the lowest 10th percentile of the population). In addition, to account for uncertainties and to ensure the most sensitive subset of the population is

protected with an adequate margin of safety, a 3-fold uncertainty factor was applied to the proposed MCLG calculation (USEPA, 2019a). More discussion on the uncertainty factor is presented in the section "Consideration of Uncertainties."

The EPA received some comments stating that the selection of the study for informing the relationship between maternal hormone levels (fT4) and IQ was inadequately described. Other comments supported the EPA's study selection. The EPA concludes that selection of the Korevaar et al. (2016) study is appropriate because that study provides the most robust data available with a clear measure of neurodevelopment that can be expressed as a function of changing maternal fT4 exposure, which is necessary to the development of the model.

BBDR and PBPK Models

The EPA received comments indicating the BBDR model was not transparent, scientifically valid, or based on robust data. The EPA disagrees. The model represents the best available peer reviewed science and uses the best available data to inform a MCLG for perchlorate. The EPA disagrees that there is a significant lack of transparency with respect to the assumptions related to the BBDR model. Appendix A of the EPA's Proposed MCLG Approaches report outlines the justification for all assumptions used in the development of the BBDR model (USEPA, 2019a). The EPA also disagrees with the assertion the BBDR model is far too uncertain to be relied upon as the basis for the derivation of the RfD. The EPA has used the best available science to calibrate the pharmacokinetic aspects of the

BBDR model. The development of the BBDR model was in response to SAB recommendations and a model was deemed to be a more refined approach to estimating a dose-response relationship between perchlorate exposure and maternal fT4 than anything that was available in the current scientific literature. The EPA disputes the claim that there are issues with the scientific validity of the BBDR model as the Agency conducted a peer review of the approach proposed and the reviewers stated the approach was "fit for purpose" to inform a MCLG for perchlorate (External Peer Reviewers for U.S. EPA, 2018, p. 2).

Consideration of Uncertainties

The EPA received comments on the Agency's use of Uncertainty Factors (UFs); with most commenters suggesting that the EPA should consider a higher UF. The EPA thoroughly considered the application of UFs when deriving the RfDs and followed guidance presented in "A review of the reference dose and reference concentration processes" (USEPA, 2002). The EPA concluded that the UFs are adequately justified and subsequently no changes have been made. Justification for each of the UFs can be found in Section 11 of the Agency's MCLG Derivation report (USEPA, 2019a).

The EPA selected a UF of 3 for inter-individual variability because the Agency specifically modeled groups within the population that are identified as likely to be at greater risk of the adverse effects from perchlorate in drinking water (i.e., the fetus of the iodide deficient pregnant mother). The EPA selected model parameters to account for the most sensitive individuals in that group (i.e., muted TSH feedback, low fT4 values, low-iodine

intake). As discussed in the MCLG Derivation report, the EPA has attempted to select the most appropriate inputs to protect the most sensitive population with an adequate margin of safety (USEPA, 2019a). The EPA has determined that the selection of a UF of 3 for inter-individual variability is justified. As described in the MCLG Derivation report, because the output from the BBDR model is specific to the sensitive population the EPA concluded that the UF of 3 is appropriate. In regards to variation in sensitivity among the members of the human population (i.e., inter-individual variability), section 4.4.5.3 of the EPA guidance "A review of the reference dose and reference concentration process" (USEPA, 2002) document states, "In general, the Technical Panel reaffirms the importance of this UF, recommending that reduction of the intraspecies UF from a default of 10 be considered only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s). Similar to the interspecies UF, the intraspecies UF can be considered to consist of both a toxicokinetic and toxicodynamic portion (i.e. 10^0.5 each)" (USEPA, 2002). Given that the BBDR model significantly accounts for differences within the human population, the full UF of 10 is not warranted.

One commenter suggested using a UF greater than 1 to account for the extrapolation of the lowest-observed adverse effect level (LOAEL) to the no-observed-adverse-effect-level (NOAEL). LOAELs and NOAELs were not identified or used by the EPA in its assessment because the Agency employed a sophisticated BBDR modeling approach, which was coupled with extrapolation to changes in IQ using linear regression, to determine a POD that would

not be expected to represent an adverse effect. Therefore, a UF of 1 is appropriate. Other commenters suggested incorporating UFs for database deficiencies. Based on the findings of the NRC report, the EPA has previously concluded that this UF was not needed for deficiencies in the perchlorate database (NRC, 2005; USEPA, 2005a). The EPA determined that a UF of 1 to account for database deficiencies is still appropriate given that the state of the perchlorate database has only increased since 2005.

C. *Occurrence Analysis*

The EPA received comments suggesting that the revised UCMR 1 data did not provide an adequate estimate of the perchlorate occurrence in drinking water systems. Some commenters indicated that the age of the collected data rendered the occurrence analysis obsolete and overestimated, since it no longer captures current lower contamination conditions that have been achieved due to mitigation measures taken in the Colorado River Basin. Other commenters criticized the EPA for replacing UCMR 1 data with compliance data for the States of California and Massachusetts.

The EPA recognizes that changes in perchlorate levels (increasing or decreasing) may have occurred in water systems since the UCMR 1 samples were collected between 2001 to 2005. The EPA updated the UCMR 1 data set to improve its accuracy in representing the current conditions for states that have enacted perchlorate regulations since the UCMR 1 monitoring was conducted. As outlined in the June 26, 2019 proposal, the EPA updated occurrence data for California and Massachusetts with current compliance data as reported

by the states. Systems from these two states that were sampled during the UCMR 1 and that had reported perchlorate detections were updated with more recently measured values taken from current compliance monitoring data from Consumer Confidence Reports and state-level perchlorate compliance monitoring data to match corresponding water systems and entry points.

The EPA has determined that the updated UCMR 1 data are the best available data collected in accordance with accepted methods on the frequency and level of perchlorate occurrence in drinking water on a national scale.

V. Conclusion

With this withdrawal of the 2011 perchlorate regulatory determination and final determination to not regulate perchlorate, the EPA announces that there will be no NPDWR for perchlorate at this time. The EPA could consider re-listing perchlorate on the CCL and could proceed to regulation in the future if the occurrence or health risk information changes. As with other unregulated contaminants, the EPA will consider addressing limited instances of elevated levels of perchlorate by working with the affected system and state, as appropriate.

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List of Subjects in 40 CFR Parts 141 and 142

Administrative practice and procedure, Chemicals, Indians-lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Andrew Wheeler,

Administrator.

DELIBERATIVE DRAFT
TO BE UPDATED FOLLOWING INTER AGENCY REVIEW

MEMORANDUM

SUBJECT: Notice of Final Action on Perchlorate
(Tier 1 Action; SAN 5555; RIN 2040-AF28) – **ACTION MEMORANDUM**

FROM: David P. Ross
Assistant Administrator (4101M)

THRU: Office of Policy (1803A)
Office of Executive Secretariat (1105A)

TO: Andrew R. Wheeler
Administrator (1101A)

PURPOSE
Attached for your signature is the action titled "Notice of Final Action on Perchlorate."

On February 11, 2011, the U.S. Environmental Protection Agency (EPA or Agency) published a determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), the EPA published the proposed National Primary Drinking Water Regulations (NPDWR) for Perchlorate and requested public comments on multiple alternative actions, including withdrawing the Agency's 2011 determination to regulate perchlorate. The EPA received approximately 1,500 comments on the proposed rule.

In this notice, the EPA is withdrawing the 2011 Regulatory Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available information.

DEADLINE/TIMELINE
Section 1412(b)(1)(A) of the Safe Drinking Water Act (SDWA) requires the EPA to issue a proposed NPDWR within 24 months of the final regulatory determination and a final NPDWR within 18 months after the proposal. However, when the EPA consulted with the Science Advisory Board (SAB) regarding a planned methodology for deriving the maximum contaminant level goal (MCLG) for perchlorate, the Agency received recommendations to develop a physiologically based pharmacokinetic model (i.e., a biologically based dose-response model (BBDR)) to predict the effects of perchlorate exposure on thyroid function in pregnant women and their children, instead. The EPA collaborated with Food and Drug Administration scientists to perform the modeling recommended by the SAB and completed the analysis and associated peer reviews in March 2018. This delayed the EPA in proposing a NPDWR within 24 months.

In February 2016, the Natural Resources Defense Council (NRDC) filed a lawsuit for failure of the EPA to perform its mandatory duties of proposing and finalizing a regulation for perchlorate in accordance with timelines provided in the SDWA. On October 18, 2016, the U.S. District Court for the Southern District of New York entered a Consent Decree, requiring the EPA to sign for publication a proposal for a MCLG and NPDWR for perchlorate in drinking water no later than October 31, 2018, and to sign for publication a final MCLG and NPDWR for perchlorate in drinking water no later than December 19, 2019. The Court later extended the deadline for the EPA to propose a MCLG and NPDWR for perchlorate in drinking water to May 28, 2019, and extended the date for signature of a final MCLG and NPDWR no later than June 19, 2020.

In compliance with the deadline established in the Consent Decree, on May 23, 2019, the Administrator signed a proposed rulemaking notice seeking public comment on a range of options regarding the regulation of perchlorate in public drinking water systems. The EPA published the proposed rule in the *Federal Register* on June 26, 2019. The public comment period for the proposal ended on August 26, 2019, and the EPA received approximately 1,500 comments.

DESCRIPTION OF THE ACTION

Perchlorate is an inorganic anion that occurs naturally. It is also manufactured as an oxidizer for rockets, missiles, and fireworks and can be an impurity in hypochlorite disinfectants. The public may be exposed to perchlorate through food and drinking water. At certain levels, perchlorate can prevent the thyroid gland from getting enough iodine, which can affect thyroid hormone production. For pregnant women with low iodine levels, sufficient changes in thyroid hormone levels may cause changes in the child's brain development. For infants, changes to thyroid hormone function can also impact brain development.

The SDWA sets forth three criteria that must be met for the EPA to issue a MCLG and promulgate a NPDWR. Specifically, the EPA must determine that (1) "the contaminant may have an adverse effect on the health of persons;" (2) "the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern;" and (3) "in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems" (SDWA 1412(b)(1)(A)).

In the attached notice, the EPA concludes that, based on new data and the Agency's analysis since the issuance of the 2011 Regulatory Determination, perchlorate does not in fact meet the statutorily prescribed criteria for regulation. The new data and analysis indicate that perchlorate does not occur in public water systems with a frequency and at levels of public health concern. Specifically, the new peer-reviewed health effects analysis resulted in the health based proposed MCLG and proposed alternative MCLGs for perchlorate that are higher concentrations in drinking water (18 – 90 µg/L) than the concentrations that the EPA considered to be levels of public health concern in the Agency's analysis for the determination to regulate in 2011 (1 – 47 µg/L). In addition, the updated occurrence analysis shows that the frequency of occurrence of perchlorate in public water systems at levels exceeding any of the alternative proposed MCLGs (0.38% – 0.02%) is significantly lower than the frequency considered in the

EPA's analysis for the 2011 Regulatory Determination (4% – 0.39%). Based on this information, the EPA is announcing the Agency's conclusion that perchlorate does not occur in public water systems "with a frequency…of public health concern" and, therefore, regulation of perchlorate does not present a "meaningful opportunity for health risk reduction for persons served by public water systems" as required for regulation under the SDWA. Accordingly, perchlorate no longer meets the statutory criteria for regulation because the EPA does not have the authority to issue a MCLG or promulgate a NPDWR for perchlorate.

Therefore, the EPA is not issuing a final MCLG or NPDWR for perchlorate. The EPA will consider addressing limited instances of elevated levels of perchlorate by working with the affected system and state, as appropriate.

STAKEHOLDER INVOLVEMENT AND ANTICIPATED RESPONSE

The EPA considered the approximately 1,500 comments that were submitted on the proposed regulation. The EPA also consulted with the National Drinking Water Advisory Committee regarding the proposed regulation. The EPA expects a variety of reactions and responses from stakeholders. The NRDC will likely sue the EPA for failure to comply with the Consent Decree and will likely challenge the Agency's authority to withdraw a Regulatory Determination. Officials from the States of California and Massachusetts, public health groups and environmental groups will likely state that a low perchlorate maximum contaminant level is needed to protect children's health. Industry groups, including the American Water Works Association, the Perchlorate Study Group, the American Chemistry Council, and the U.S. Chamber of Commerce will support the decision not to regulate perchlorate in drinking water. These groups will agree with the EPA's determinations that perchlorate does not occur frequently at levels of public health concern and there is not a meaningful opportunity for health risk reduction for persons served by public water systems.

INTERNAL DEVELOPMENT AND REVIEW PROCESS

The attached notice reflects the direction provided by the Administrator in the Options Selection and follow-up meetings held on January 9 and March 18, 2020. The Office of Water (OW) convened a Final Agency Review meeting for this action on May 7, 2020. The following offices concurred without comment: the Office of Research and Development, the Office of Land and Emergency Management, the Office of Air and Radiation, and the Office of Chemical Safety and Pollution Prevention. The following offices concurred with comment: the Office of General Counsel (OGC), the Office of Policy (OP), and the Office of Children's Health Protection (OCHP). OW has incorporated revisions identified in the comments from the OGC. OW has also incorporated most of the suggested revisions identified by OP, the key exception being that we are not incorporating OP's recommendation to not list the cost benefit analysis as a factor in the decision to withdraw the regulatory determination. OW has worked with OGC to incorporate language that clarifies that this does not set a precedent for future regulatory determinations. OW is not incorporating the majority of recommendations made by OCHP, which address the health effects and occurrence analysis and are issues we have evaluated previously, including in response to OCHP's input on the proposal and in response to public comments.

INTERAGENCY REVIEW

The Office of Management and Budget initiated review of the *Federal Register* notice: "Notice of Final Action on Perchlorate" on [date placeholder].

PEER REVIEW

For the proposed rulemaking, OW followed the EPA's Peer Review Handbook and Agency policy titled "Conflicts of Interest Review Process for Contractor-Managed Peer Reviews of EPA HISA and ISI Documents" when conducting the peer review of models used to derive the proposed MCLGs for perchlorate. The EPA convened an independent peer review panel to evaluate the BBDR models in 2017 and a second, expert peer review panel in 2018 to evaluate the update of the BBDR model and approaches to link the BBDR model output to neurodevelopment endpoints in epidemiology studies to derive an MCLG. The EPA also sought input from the SAB, as required by the SDWA, prior to developing the proposed MCLGs.

RECOMMENDATION

I recommend that you sign the attached *Federal Register* notice titled "Notice of Final Action on Perchlorate."

Attachments (2)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF WATER

MEMORANDUM

SUBJECT: Transmittal of the Notice of Final Action on Perchlorate (Tier 1 Action; SAN 5555; RIN 2040-AF28) to the Office of Management and Budget for Executive Order 12866 Review

FROM: Charlotte Bertrand,
Deputy Assistant Administrator

TO: Brittany Bolen, Associate Administrator
Office of Policy

Attached for the Office of Policy's review and transmittal to the Office of Management and Budget (OMB) for Executive Order 12866 interagency review is a *Federal Register* notice titled: "Notice of Final Action on Perchlorate."

On February 11, 2011, the U.S. Environmental Protection Agency (EPA or Agency) published a determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), the EPA published the proposed National Primary Drinking Water Regulations for Perchlorate and requested public comments on multiple alternative actions, including withdrawing the 2011 determination to regulate perchlorate. The EPA received approximately 1,500 comments on the proposed rule. In the attached notice, the EPA is withdrawing the 2011 Regulatory Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available science.

I request that the Office of Policy seek an expedited interagency review in accordance with Executive Order 12866 to meet a consent decree deadline for signature of the final action by June 19, 2020.

If you have any questions, please contact me or have your staff contact Samuel Hernandez at 202-564-1735.

Attachments

Message

From: Mclain, Jennifer [Mclain.Jennifer@epa.gov]
Sent: 12/2/2019 10:40:17 PM
To: Ross, David P [ross.davidp@epa.gov]
CC: Forsgren, Lee [Forsgren.Lee@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Wildeman, Anna [wildeman.anna@epa.gov]; Best-Wong, Benita [Best-Wong.Benita@epa.gov]; Aguirre, Janita [Aguirre.Janita@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Burneson, Eric [Burneson.Eric@epa.gov]; Nagle, Deborah [Nagle.Deborah@epa.gov]
Subject: Perchlorate - Administrator's Option Selection Briefing
Attachments: Option Selection for Perchlorate 12-2-19 v2.docx

Dave

As we discussed at the 11/14 OGWDW Biweekly meeting, we developed the attached Option Selection briefing document for the Administrator's consideration. As you recommended, tomorrow we are briefing OLEM on the comments we received on the proposed regulation and the options for a final action. We plan to discuss the potential impacts to their program under different options (these impacts are included in the briefing document). The meeting invitation is on Peter Wright's calendar although we are not certain if he will attend. We will follow up with you regarding next steps with the Administrator after our meeting with OLEM.

Jennifer

Message

From: McLain, Jennifer L. [McLain.Jennifer@epa.gov]
Sent: 5/19/2020 1:17:18 PM
To: Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]
CC: Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Braschayko, Kelley [braschayko.kelley@epa.gov]; Tiago, Joseph [Tiago.Joseph@epa.gov]; Aguirre, Janita [Aguirre.Janita@epa.gov]
Subject: FW: Notice of Final Action on Perchlorate
Attachments: Perchlorate Action Memo 5-18-20.cb.srmd.docx; Draft Perchlorate Final Action FRN 5-18-20 v1 Redline.cb.srmd.docx

Charlotte – the attached provide edits and responses to your questions. We will start the process to formally send to OW for submittal to OP.

Thanks
Jennifer

From: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Sent: Monday, May 18, 2020 5:29 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Braschayko, Kelley <braschayko.kelley@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Thanks – couple of bubble box questions and then I had one redline edit I added to the Notice.

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Monday, May 18, 2020 3:01 PM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Braschayko, Kelley <braschayko.kelley@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Aguirre, Janita <Aguirre.Janita@epa.gov>
Subject: FW: Notice of Final Action on Perchlorate

Charlotte – as agreed, I'm sending you the draft final perchlorate FRN for review. The redline includes the changes made since the FAR. I'm also including the draft Action Memo. Please let us know if your preference is to have these submitted to OW through CMS now or after you have reviewed. Let me know if you want to talk.

Jennifer

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, May 18, 2020 2:48 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Subject: FW: Notice of Final Action on Perchlorate

Jennifer:

Attached for transmission to OW are revised versions of the FRN for the Perchlorate Final Action. There is both a clean and track changes version that includes edits made since initiating FAR (including the edits you asked for on Saturday and adding 3 more SAB recommendations to page 14 that were in the proposal but were not included in the draft we provided you on Friday). Also please find clean version of the transmittal memo from you to Dave Ross and the Action memo incorporating your edits.

Please note that there is also a redline version of the Action Memo for you to see the responses to your comments on the document. I do not recommend transmitting that memo to OW.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, May 18, 2020 2:18 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Hi Eric,

Attached are the revised Redline and Clean versions of the Perchlorate FR Notice. Once we are ready for OP's submittal to OMB let me know and I will provide a version that adheres to OP's file name formatting guidelines.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, May 18, 2020 1:14 PM
To: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Sam

1. Change the title please. This was requested by OGC at Sr. Leadership levels.
2. Provide the same level of detail on the SAB recommendations as was included in the proposal.
3. I don't think the HRRCA text is necessary and do not want to add it at this stage since there are OGC edits that already make this clear.

Eric

From: Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Sent: Monday, May 18, 2020 12:41 PM
To: Burneson, Eric <Burneson.Eric@epa.gov>

Cc: Christ, Lisa <Christ.Lisa@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Hi Eric,

Here is a revised Redline of the document (from FAR). We had a few questions/issues for your consideration about the attached file. Specifically:,

1- Page #1, Notice Tittle: We did not accept the edits to the notice tittle. Because, the tittle of the notice was specifically crafted by OGC to capture the multiple actions EPA is taking. Suggest consulting with OGC before modifying this tittle.
2- Page #14, SAB Recommendations: SAB provided 4 main recommendations in 2013 but we only listed the first recommendation. Please advise if we should list all 4 recommendations here or not.
3- Page #26, Missing HRRCA Text: This language was offered by TAB in its 5-13-20 version of the draft FRN, but it did not show up in the version provided by OGWDW with Eric's & Jennifer's comments. We have inserted the language here for the reviewer's consideration. Please advise if we should keep it.

Once you provide your feedback, I will modify the redline version and also provide a Clean copy for transmittal.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Monday, May 18, 2020 8:42 AM
To: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>
Cc: McLain, Jennifer L. <McLain.Jennifer@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: FW: Notice of Final Action on Perchlorate

Lisa and Sam
Attached are Jennifer's comments and edits on the draft FRN. I have responded to her questions in the attached and made some additional edits. Can you please get a revised clean version and another redline version that compares this document and the version that was distributed to FAR?
Thanks for your work on this.
Eric

From: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Sent: Saturday, May 16, 2020 11:39 AM
To: Burneson, Eric <Burneson.Eric@epa.gov>
Subject: RE: Notice of Final Action on Perchlorate

Looks very good. See p. 6 for my only concern w/the revisions.

From: Burneson, Eric <Burneson.Eric@epa.gov>
Sent: Friday, May 15, 2020 5:03 PM
To: McLain, Jennifer L. <McLain.Jennifer@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Hernandez-Quinones, Samuel <Hernandez.Samuel@epa.gov>; Tiago, Joseph <Tiago.Joseph@epa.gov>; Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>
Subject: Notice of Final Action on Perchlorate

Jennifer

Attached for your approval and transmittal to the Office of Water for their approval and transmittal to the Office Policy for initiation of interagency review is a *Federal Register* notice titled: "Notice of Final Action on Perchlorate." Also attached for your review are a draft transmittal memo from you to the Assistant Administrator of Water, a draft Action Memorandum and a track changes version of the FR notice that denotes the changes made as a result of Final Agency Review.

On February 11, 2011, the EPA published a determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), the EPA published the proposed National Primary Drinking Water Regulation for Perchlorate and requested public comments on multiple alternative actions, including withdrawing the 2011 determination to regulate perchlorate. The EPA received approximately 1,500 comments on the proposed rule. In the attached notice, the EPA is withdrawing the 2011 Regulatory Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available information.

I recommend that you approve and transmit the attached notice to the Office of Water for their review, approval and transmission to the Office of Policy to initiate interagency review in accordance with Executive Order 12866. If you need additional information or have questions pertaining to any aspect of this notice, please call me or have your staff contact Samuel Hernandez at 202-564-1735.

Eric Burneson, P.E.
Director of Standards and Risk Management
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
202 564 5250

6560-50-P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 141 and 142

[EPA-HQ-OW-2018-0780, EPA–HQ–OW–2008–0692, EPA–HQ–OW– 2009–0297; FRL-XXXX-XX-OW]

RIN 2040-AF28

Drinking Water: Notice of ~~Withdrawal of the 2011 Perchlorate Regulatory Determination and Publication of the~~ **Final** Action~~Regulatory Determination~~ **on Perchlorate**

AGENCY: Environmental Protection Agency (EPA).

ACTION: ~~Withdrawal of Regulatory Determination and~~ Final Action ~~Regulatory Determination~~.

Commented [BC1]: Will this show up publicly in ROCIS?

Commented [BE2R1]: This information is used to populate the Stage field on the RegInfo.gov site at least that is how it is used for Lead Free. I have edited this information to avoid disclosing the outcome but its not clear if this is going to work for the system

SUMMARY: The Environmental Protection Agency (EPA) is announcing its withdrawal of the 2011 determination to regulate perchlorate in accordance with the Safe Drinking Water Act (SDWA). On February 11, 2011 ~~(76 FR 7762),~~ the ~~Agency~~EPA published a *Federal Register* notice in which the ~~EPA~~Agency determined that perchlorate met the SDWA's criteria for regulating a contaminant. On June 26, 2019 ~~(84 FR 30524),~~ the EPA published a proposed national primary drinking water regulation (NPDWR) for perchlorate and requested public comments on multiple alternative regulatory actions, including the alternative of withdrawing the 2011 regulatory determination for perchlorate. The ~~Agency~~EPA received approximately 1,500 comments on the proposed rule. The EPA has considered these public comments and based on

the best available information the Agency is withdrawing the 2011 regulatory determination and is making a final determination to not to regulate perchlorate. The Agency EPA has determined that perchlorate does not occur with a frequency and at levels of public health concern, and that regulation of perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems.

DATES: For purposes of judicial review, the regulatory determination in this document is issued as of *[insert date of publication in the* Federal Register*]*.

FOR FURTHER INFORMATION CONTACT: Samuel Hernandez, Office of Ground Water and Drinking Water, Standards and Risk Management Division (Mail Code 4607M), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460; telephone number: (202) 564-1735; email address: hernandez.samuel@epa.gov.

SUPPLEMENTARY INFORMATION: This notice is organized as follows:

I. General Information

A. Does This Action Apply to Me?

This action will not impose any requirements on anyone. Instead, this action notifies interested parties of the EPA's withdrawal of the 2011 regulatory determination for perchlorate and the final regulatory determination to not regulate perchlorate based on new information.

This notice also provides a summary of the major comments received on the June 26, 2019 (84 FR 30524) proposed NPDWR for perchlorate.

B. How can I get Copies of this Document and other Related Information?

The EPA has established a docket for this action under Docket ID No. EPA–HQ–OW–2018–0780. Publicly available docket materials are available electronically at [HYPERLINK "http://www.regulations.gov/docket?D=EPA-HQ-OW-2018-0780"].

II. Background

A. What is Perchlorate?

Perchlorate is a negatively charged inorganic ion that is comprised of one chlorine atom bound to four oxygen atoms (ClO_4-), which is highly stable and mobile in the aqueous environment. Perchlorate comes from both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas. It is also produced in the United States, and the most common compounds include ammonium perchlorate and potassium perchlorate used primarily as oxidizers in solid fuels to power rockets, missiles, and fireworks. Perchlorate can also result from the degradation of hypochlorite solutions used for water disinfection. The degradation into perchlorate occurs when hypochlorite solutions are improperly stored and handled. For the general population, most perchlorate exposure is through the ingestion of contaminated food or drinking water. At certain levels, perchlorate can prevent the thyroid gland from getting enough iodine, which can affect thyroid hormone

production. For pregnant women with low iodine levels, sufficient changes in thyroid hormone levels may cause changes in the child's brain development. For infants, changes to thyroid hormone function can also impact brain development.

B. What is the purpose of this action?

The purpose of ~~today's~~ this action is to publish the EPA's notice to withdraw the 2011 regulatory determination and issue a final determination to not regulate perchlorate in drinking water. This notice presents the EPA's basis for this withdrawal and final regulatory determination, and the EPA's response to key issues raised by commenters in response to the June 26, 2019 (84 FR 30524) proposed rule (referred to hereinafter as "the 2019 proposal").

C. What is the EPA's statutory authority for this action?

The SDWA sets forth three criteria that must be met for the EPA to issue a maximum contaminant level goal (MCLG) and promulgate a national primary drinking water regulation (NPDWR). Specifically, the Administrator must determine that (1) "the contaminant may have an adverse effect on the health of persons"; (2) "the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern"; and (3) "in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by ~~the~~ public water systems" (SDWA 1412(b)(1)(A)).

The EPA has determined, based on ~~new~~ data and analysis since the issuance of the 2011 regulatory determination, that perchlorate does not in fact meet the statutorily-prescribed criteria

for regulation. As described in Sections III & VI of the 2019 proposal, the ~~new~~ data and analysis in the record indicate that perchlorate does not occur in public water systems with a frequency and at levels of public health concern. Specifically, the ~~new~~ peer-reviewed health effects analysis ~~yields a health based proposed MCLG and proposed alternative MCLGs for~~ indicates that the concentration of perchlorate ~~that are higher concentrations in drinking water (18—90 µg/L) than the concentrations that the EPA considered to be~~ representing the proposaled MCLG alternatives for levels of public health concern ~~in~~ (18-90 µg/L) is higher than the concentration considered in issuance of the ~~analysis for the 2011 regulatory~~ determination ~~to regulate in 2011~~ (1-47 µg/L) (USEPA, 2019a). In addition, based on an evaluation of the nationally representative UCMR 1 systems, the updated occurrence analysis shows that the frequency of occurrence of perchlorate in public water systems at levels exceeding any of the alternative proposed MCLGs ~~(0.38%—0.02%)~~ is significantly lower (0.38% - 0.02%) than the frequency considered in the analysis for the 2011 regulatory determination (4% - 0.39%) (USEPA, 2019b). The EPA estimates that, even at the most stringent regulatory level considered in the 2019 proposal, (18 µg/L), not more than 15 systems (0.03% of all water systems in the U.S.) would need to take action to reduce levels of perchlorate. Based on this information, the EPA determines that perchlorate does not occur in public water systems "with a frequency…of public health concern" and thus does not meet the second criterion of the three required for regulation under the SDWA. In addition, while the third criterion is "in the sole judgement of the Administrator," the low occurrence provides ample support for the EPA's conclusion that the regulation of perchlorate does not present a

"meaningful opportunity for health risk reduction for persons served by public water systems," within the meaning of 1412(b)(1)(A)(iii). Accordingly, because perchlorate no longer meets the statutory criteria for regulation, the EPA does not have the authority to issue a MCLG or promulgate a NPDWR for perchlorate.

The EPA's decision to withdraw the regulatory determination is supported by the legislative history underlying the 1996 amendments to the SDWA, which repealed the ~~blanket rule requiring~~statutory requirement for the EPA to regulate an additional 25 contaminants every 3 years and replaced it with the current requirement for the EPA to determine whether regulation is warranted for ~~5~~five contaminants every ~~5~~five years. In describing the need for such amendment, the legislative history points to the view expressed at the Committee Hearing that "the current law is a one-size-fits-all program. It forces our water quality experts to spend scarce resources searching for dangers that often do not exist rather than identifying and removing real health risks from our drinking water" (S. Rep. 104-169 (1995) at 12). This amendment reflected Congress' clear intent that the EPA prioritize actual health risks in determining whether to regulate any particular contaminant. *See id* at 12 (noting that the amendment "repeals the requirement that the EPA regulate an additional 25 contaminants every 3 years replacing it with a new selection process that gives the EPA the discretion to identify contaminants that warrant regulation in the future").

The EPA's decision to withdraw the regulatory determination is also consistent with Congress' direction to prioritize the SDWA decisions based on the best available public health

information. *See* 1412(b)(1)(B)(ii)(II) (findings supporting a determination to regulate "shall be based on the best available public health information"); 1412(b)(2)(A) (requiring that the EPA use "the best available, peer-reviewed science and supporting studies…" in carrying out any actions under this section). Although the EPA determined in 2011 that perchlorate met the criteria for regulation, new data and analysis developed by the EPA Agency as part of the 2019 proposal demonstrate that the occurrence and health effects information used as the basis for the 2011 determination no longer constitute "best available information," are no longer accurate and no longer support the Agency's prioritization of perchlorate for regulation. Accordingly, not only is EPA not authorized to issue a MCLG or promulgate a NPDWR for perchlorate, but it would not be in the public interest to do so.

The EPA recognizes that the Act does not include a provision explicitly authorizing withdrawal of a regulatory determination. However, such authority is inherent in the authority to issue a regulatory determination under 1412(b)(1)(B)(ii)(II), particularly given the requirement that such determination be based on the "best available public health information," as discussed above. Accordingly, the EPA must have the inherent authority to withdraw a regulatory determination if the underlying information changes between regulatory determination and promulgation. ~~Particularly~~ In light of its concern that the EPA focus new contaminant ~~regulation~~regulations on priority health concerns, Congress could not have intended that the EPA's regulatory decision-making be hamstrung by older data when newer, more accurate scientific and public health data are available, especially when those data demonstrate that

regulation of a new contaminant would not ~~be~~present a meaningful opportunity for health risk reduction.

Moreover, the EPA notes that the statute specifically provides that a decision to not ~~to~~ regulate a contaminant is a final Agency action subject to judicial review. The SDWA, section 1412(b)(1)(B)(ii)(IV). ~~Congress'~~Congress could have – but did not – specify the same with respect to determinations to regulate. Congress also did not explicitly prohibit the EPA from withdrawing or modifying a regulatory determination. Congress' silence with respect to ~~regulatory~~ determinations to regulate suggests that Congress intended that such ~~determinations are~~a determination is not ~~in fact~~itself a final agency ~~actions subject to judicial review~~action, but rather, a preliminary ~~decisions to regulate~~step in a decision-making process culminating in a NPDWR and thus, subject to reconsideration based on new data and analysis considered during the 36 month promulgation process specified in the statute. Accordingly, reconsideration of this preliminary finding – and withdrawal of the determination based on subsequent analysis mandated for NPDWR development – is fully consistent with the statutory decision-making framework.

D. Statutory Framework and Perchlorate Regulatory History

Section 1412(b)(1)(B)(i) of the SDWA requires the EPA to publish every five years a Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to federal drinking water regulations. The EPA uses the CCL to identify priority contaminants for

regulatory decision-making and information collection. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA included perchlorate on the first, second, and third CCLs published in 1998 (63 FR 10274), 2005 (70 FR 9071), and 2009 (74 FR 51850).

The ~~Agency~~ EPA collects data on the CCL contaminants to better understand their potential health effects and to determine the levels at which they occur in public water systems. The SDWA, section 1412(b)(1)(B)(ii) requires that, every five years, the EPA, after consideration of public comment, issue a determination of whether or not to regulate at least five contaminants on each CCL. For any contaminant that the EPA determines meets the SDWA criteria for regulation, under the SDWA, section 1412(b)(1)(E), the EPA must propose a NPDWR within two years and promulgate a final regulation within 18 months of the proposal (which may be extended by 9 additional months).

As part of its responsibilities under the SDWA, the EPA implements section 1445(a)(2), "Monitoring Program for Unregulated Contaminants." This section requires that once every five years, the EPA issue a list of no more than 30 unregulated contaminants to be monitored by public water systems. This monitoring is implemented through the Unregulated Contaminant Monitoring Rule (UCMR), which collects data from community water systems ~~(CWS)~~ and non-transient, non-community water systems ~~(NTNCWS)~~. The first four UCMRs collected data from a census of large water systems (serving more than 10,000 people) and from a statistically representative sample of small water systems. On September 17, 1999, the EPA published its first UCMR (64 FR 50556), which required all large systems and a representative sample of

small systems to monitor for perchlorate and 25 other contaminants (USEPA, 1999). Water system monitoring data for perchlorate was collected from 2001 to 2005.

The EPA and other federal agencies asked the National Research Council (NRC) to evaluate the health implications of perchlorate ingestion. In its 2005 report, the NRC concluded that perchlorate exposure inhibits the transport of iodide[1] into the thyroid by a protein molecule known as the sodium/iodide symporter (NIS), which may lead to decreases in two thyroid hormones, thyroxine (T3) and triiodothyronine (T4), and increases in thyroid-stimulating hormone (TSH) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, the NRC concluded that the

[1] For the purposes of this notice, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

most sensitive population to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" (p. 178). The EPA established a reference dose (RfD) consistent with the NRC's recommended RfD of 0.7 µg/kg/day for perchlorate. The reference dose is an estimate of a human's daily exposure to perchlorate that is likely to be without an appreciable risk of adverse effects. This RfD was based on a study [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3u94lt6me","properties":{"formattedCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","plainCitation":"(Greer, Goodman, Pleus, & Greer, 2002)","noteIndex":0},"citationItems":[{"id":387,"uris":["http://zotero.org/groups/945096/items/6AKUNIX6"],"uri":["http://zotero.org/groups/945096/items/6AKUNIX6"],"itemData":{"id":387,"type":"article-journal","title":"Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans","container-title":"Environmental Health Perspectives","page":"927","volume":"110","issue":"9","author":[{"family":"Greer","given":"Monte A."},{"family":"Goodman","given":"Gay"},{"family":"Pleus","given":"Richard C."},{"family":"Greer","given":"Susan E."}],"issued":{"date-parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] of perchlorate's inhibition of radioactive iodine uptake in healthy adults and the application of an uncertainty factor of 10 for intraspecies variability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0oHz805e","properties":{"formattedCitation":"(USEPA,

2005b)","plainCitation":"(USEPA,
2005b)","noteIndex":0},"citationItems":[{"id":980,"uris":["http://zotero.org/groups/945096/item
s/LHANJBR6"],"uri":["http://zotero.org/groups/945096/items/LHANJBR6"],"itemData":{"id":9
80,"type":"article","title":"Integrated Risk Information System (IRIS) Chemical Assessment
Summary: Perchlorate (ClO4-) and Perchlorate Salts","publisher":"USEPA National Center for
Environmental Assessment","author":[{"literal":"USEPA"}],"issued":{"date-
parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}].

In October 2008, the EPA published a preliminary regulatory determination to not to regulate perchlorate in drinking water and requested public comment (73 FR 60262). In that preliminary determination, the EPA found that perchlorate did not occur with a frequency and at levels of public health concern and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA derived and used a Health Reference Level (HRL) of 15 µg/L based on the RfD of 0.7 µg/kg/day and body weight and exposure information for pregnant women in making this conclusion [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"FZ6WMtAv","properties":{"formattedCitation":"(USEPA,
2008a)","plainCitation":"(USEPA,
2008a)","noteIndex":0},"citationItems":[{"id":934,"uris":["http://zotero.org/groups/945096/item
s/HBX88QM9"],"uri":["http://zotero.org/groups/945096/items/HBX88QM9"],"itemData":{"id":

934,"type":"article-journal","title":"Drinking water: Preliminary regulatory determination on perchlorate","container-title":"Federal Register","volume":"73","issue":"198","abstract":"SUMMARY: This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water Act (SDWA). The Agency has determined that a national primary drinking water regulation (NPDWR) for perchlorate would not present \"a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). EPA included perchlorate on the first and second CCLs that were published in the Federal Register on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the Federal Register on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with technical information that they may use in addressing local contamination.","ISSN":"ISSN 0097-6326 EISSN 2167-2520","shortTitle":"Federal Register","journalAbbreviation":"Fed. Reg.","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-

parts":[["2008"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Using the UCMR 1 occurrence data, the EPA estimated that less than 1% of drinking water systems (serving approximately 1 million people) had perchlorate levels above the HRL of 15 µg/L. Based on this information the ~~Agency~~EPA found that perchlorate did not occur ~~frequently~~at a frequency and at levels of public health concern. The EPA also determined there was not a meaningful opportunity for a NPDWR for perchlorate to reduce health risks.

In August 2009, the EPA published a supplemental request for comment with new analysis that derived potential alternative Health Reference Levels (HRLs) for 14 life stages, including infants and children. The analysis used the RfD of 0.7 µg/kg/day and life stage-specific bodyweight and exposure information, resulting in comparable perchlorate concentrations in drinking water, based on life stage, of between 1 µg/l to 47 µg/l (74 FR 41883; USEPA, 2009).

~~On~~In February 11, 2011, the EPA published its determination to regulate perchlorate (76 FR 7762; USEPA, 2011) after careful consideration of public comments on the October 2008 and August 2009 notices. The ~~Agency~~EPA found at that time that perchlorate may have an adverse effect on the health of persons, it is known to occur in public drinking water systems with a frequency and at levels that present a public health concern, and regulation of perchlorate presented a meaningful opportunity for health risk reduction for persons served by public water systems. The ~~Agency~~EPA stated then that: "*Based on the data in Table 1 and the range of potential alternative HRLs, EPA has determined that perchlorate is known to occur or there is a*

substantial likelihood that it will occur with a frequency and at levels of public health concern."(USEPA, 2011, p. 7765). The EPA found that as many as 16 million people could potentially be exposed to perchlorate at levels of concern, up from 1 million people originally estimated in the 2008 notice.

As a result of the determination, and as required by the SDWA, section 1412(b)(1)(E), the EPA initiated the process to develop a MCLG and a NPDWR for perchlorate.

In September 2012, the U.S. Chamber of Commerce (the Chamber) submitted to the EPA a Request for Correction under the Information Quality Act regarding the EPA's regulatory determination. In the request, the Chamber claimed that the UCMR 1 data used in the EPA's occurrence analysis did not comply with data quality guidelines and were not representative of current conditions. In response to this request, the EPA reassessed the data and removed certain source water samples that could be paired with appropriate follow-up samples located at the entry point to the distribution system. The EPA also updated the UCMR 1 data in the analysis for systems in California and Massachusetts, using state compliance data to reflect current occurrence conditions after state regulatory limits for perchlorate were implemented.

As required by section 1412(d) of the SDWA, as part of the NPDWR development process, the EPA requested comments from the Science Advisory Board (SAB) in 2012, seeking guidance on how best to consider and interpret the life stage information, the epidemiologic and biomonitoring data since the NRC report, physiologically-based pharmacokinetic (PBPK)

analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. In May 2013, the SAB recommended that the EPA:

- derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling based upon its mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters;
- expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition—to thyroid hormone changes—and finally to neurodevelopmental impacts; and
- "Extend the [BBDR] model expeditiously to . . . provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB for the U.S. EPA, 2013, p. 19).

To address the SAB recommendations, the EPA revised an existing PBPK/PD model that describes the dynamics of perchlorate, iodide, and thyroid hormones in a woman during the third trimester of pregnancy (Lumen, Mattie, & Fisher, 2013; USEPA, 2009b). The EPA also created its own Biologically Based Dose Response (BBDR) models that included the additional sensitive

life stages identified by the SAB, *i.e.*, breast- and bottle-fed neonates and infants (SAB for the U.S. EPA, 2013, p. 19).

To determine whether the Agency had implemented the SAB recommendations for modeling thyroid hormone changes, the EPA convened an independent peer review panel to evaluate the BBDR models in January 2017 (External Peer Reviewers for USEPA, 2017). The EPA considered the recommendations from the 2017 peer review and made necessary model revisions to increase the scientific rigor of the model and the modeling results.

The EPA convened a second independent peer review panel in January 2018 to evaluate the revisions to the BBDR model. The EPA also presented several approaches to link the thyroid hormone changes in a pregnant mother predicted by the BBDR model to neurodevelopmental effects using evidence from the epidemiological literature (External Peer Review for U.S. EPA, 2018).

In response to a lawsuit brought to enforce the deadlines in the SDWA, section 1412(b)(1)(E), on October 18, 2016, the U.S. District Court for the Southern District of New York entered a consent decree, requiring the EPA to sign for publication a proposal for a MCLG and NPDWR for perchlorate in drinking water no later than October 31, 2018, and to sign for publication a final MCLG and NPDWR for perchlorate in drinking water no later than December 19, 2019. The deadline for the EPA to propose a MCLG and NPDWR for perchlorate in drinking water was later extended to May 28, 2019, and the date for signature of a final MCLG and

NPDWR was extended to be no later than June 19, 2020. The consent decree is available in the docket for today'sthis action.

In compliance with the deadline established in the consent decree, on May 23, 2019, the EPA Administrator signed a proposed rulemaking notice seeking public comment on a range of options regarding the regulation of perchlorate in public drinking water systems. The proposed rulemaking notice was published in the *Federal Register* on June 26, 2019. 84 Fed. Reg. 30524. The EPA proposed a NPDWR for perchlorate with aan MCL and MCLG of 56 µg/L. The proposed MCLG of 56 µg/L was based on avoiding a 2 point IQ decrement associated with exposure to perchlorate in drinking water during the most sensitive life stage (the fetus) within a specific segment of the population (iodine deficient pregnant women).

The AgencyEPA also requested comment on two alternative MCL/MCLG values of 18 µg/L and 90 µg/L, respectively. These alternatives were based upon avoiding 1 point and 3 point IQ decrements respectively, associated with perchlorate exposure. Additionally, the EPA requested comment on whether the 2011 regulatory determination should be withdrawn, based on new information including updated occurrence data on perchlorate in drinking water and new analysis of the concentration of perchlorate in drinking water that represents a level of health concern.

III. Withdrawal of the 2011 Regulatory Determination and Final Determination to Not Regulate Perchlorate

In determining whether to regulate a particular contaminant, the EPA must follow the criteria mandated by the 1996 SDWA Amendments. Specifically, in order to issue a MCLG and NPDWR for perchlorate, the EPA must determine that perchlorate "may have an adverse effect on the health of persons," that perchlorate occurs at "a frequency and at levels of public health concern" in public water systems, and that regulation of perchlorate in drinking water systems "presents a meaningful opportunity for health risk ~~reductions~~reduction for persons served by public water systems." The SDWA, section 1412(b)(1)(A). In preparing the 2019 proposal for perchlorate, the EPA updated and improved information on the levels of public health concern and the frequency and levels of perchlorate in public water systems. The following is the EPA's reassessment of the regulatory determination criteria applied to the ~~improved~~best available health science and occurrence data ~~available~~ for perchlorate.

A. May perchlorate have an adverse effect on the health of persons?

Yes, perchlorate may have adverse health effects. The perchlorate anion is biologically significant specifically with respect to the functioning of the thyroid gland. Perchlorate can interfere with the normal functioning of the thyroid gland by inhibiting the transport of iodide into the thyroid, resulting in a deficiency of iodide in the thyroid. Perchlorate inhibits (or blocks) iodide transport into the thyroid by chemically competing with iodide, which has a similar shape and electric charge. The transfer of iodide from the blood into the thyroid is an essential step in

the synthesis of thyroid hormones. Thyroid hormones play an important role in the regulation of metabolic processes throughout the body and are also critical to developing fetuses and infants, especially for brain development. Because the developing fetus depends on an adequate supply of maternal thyroid hormones for its central nervous system development during the first and second trimester of pregnancy, iodide uptake inhibition from perchlorate exposure has been identified as a concern in connection with increasing risk of neurodevelopmental impairment in fetuses of pregnant women with low dietary iodine. Poor iodide uptake and subsequent impairment of the thyroid function in pregnant and lactating women have been linked to delayed development and decreased learning capability in their infants and children (NRC, 2005). Therefore, the EPA continues to find that perchlorate may have an adverse effect on the health of persons.

B. Is perchlorate known to occur or is there a substantial likelihood that perchlorate will occur in public water systems with a frequency and at levels of public health concern?

The EPA has determined that perchlorate does not occur at with a frequency and at levels of public health concern in public water systems. The EPA has made this determination by comparing the best available data on the occurrence of perchlorate in public water systems to potential MCLGs for perchlorate.

In past regulatory determinations, the EPA has identified HRLs as benchmarks against which the EPA compares the concentration of a contaminant found in public water systems to determine if it is occurs at levels of public health concern. For the 2011 regulatory determination the EPA identified potential HRLs values ranging from 1 to 47 µg/L for 14 different life-stages.

These HRLs were not final decisions about the level of perchlorate in drinking water that is ~~necessary to protect any particular population~~ without adverse effects. For the 2019 proposal, the EPA derived three potential MCLGs for perchlorate of 18, 56, and 90 µg/L for the most sensitive life- stage ~~utilizing~~using the best available peer reviewed science in accordance with the SDWA. ~~The proposed~~After considering public comment, the EPA used these potential MCLGs ~~as~~as the levels of public health concern ~~used~~in assessing the frequency of occurrence of perchlorate in this regulatory determination. These MCLGs were set at levels to avoid IQ decrements of 1, 2, and 3 points respectively in the most sensitive life stage, the children of hypothyroxinemic women with low iodine intake. The EPA proposed an MCLG of 56 µg/L, and alternative MCLG values of 18 and 90 µg/L.

The rationale used in deriving the numerical values is presented in greater detail in the EPA's technical support document titled "Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" (USEPA, 2019b).

The EPA compared these potential MCLG values to the updated perchlorate UCMR 1 occurrence data set. A comprehensive description of the perchlorate occurrence data is presented in Section VI of the 2019 proposal. It is also available in the "Perchlorate Occurrence and Monitoring Report" (USEPA, 2019a).

The occurrence data for perchlorate ~~was~~were collected from 3,865 PWSs between 2001 and 2005 under the UCMR 1. ~~The Agency has~~In the 2019 proposal, the EPA modified ~~is~~the UCMR 1 data set in response to concerns raised by stakeholders regarding the data quality and to

represent current conditions in California and Massachusetts, which have enacted perchlorate regulations since the UCMR 1 data waswere collected. Massachusetts promulgated a drinking water standard for perchlorate of 2 µg/L in 2006 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8DPpSrv3","properties":{"formattedCitation":"(MassDEP, 2006)","plainCitation":"(MassDEP, 2006)","noteIndex":0},"citationItems":[{"id":151,"uris":["http://zotero.org/groups/945096/items/9893MBZH"],"uri":["http://zotero.org/groups/945096/items/9893MBZH"],"itemData":{"id":151,"type":"personal_communication","title":"Letter to Public Water Suppliers concerning new perchlorate regulations","URL":"https://www.mass.gov/lists/perchlorate-background-information-and-standards#perchlorate---final-standards-","author":[{"literal":"MassDEP"}],"issued":{"date-parts":[["2006"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and California promulgated a drinking water standard of 6 µg/L in 2007 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cfr6HNhg","properties":{"formattedCitation":"(California Department of Public Health, 2007)","plainCitation":"(California Department of Public Health, 2007)","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/groups/945096/items/RA45NKLQ"],"uri":["http://zotero.org/groups/945096/items/RA45NKLQ"],"itemData":{"id":150,"type":"personal_communication","title":"State Adoption of a Perchlorate Standard","URL":"https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/docum

ents/perchlorate/AdoptionMemotoWaterSystems-10-2007.pdf","author":[{"literal":"California Department of Public Health"}],"issued":{"date-parts":[["2007"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Systems in these states are now required to keep perchlorate levels in drinking water below their state limits. As discussed below, the EPA finds that perchlorate levels in drinking water and sources of drinking water have decreased since the ~~UCMR1~~UCMR 1 data collection. The main factors contributing to the decrease in perchlorate levels are the promulgation of drinking water regulations for perchlorate in California and Massachusetts and the ongoing remediation efforts in the state of Nevada to address perchlorate contamination in groundwater adjacent to the lower Colorado River upstream of Lake Mead.

To update the occurrence data for systems sampled during UCMR 1 from California and Massachusetts, the EPA identified all systems and corresponding entry points which had reported perchlorate detections in UCMR 1. Once the systems and entry points with detections were appropriately identified, the EPA then used a combination of available data from Consumer Confidence Reports (CCRs) and perchlorate compliance monitoring data from California (https://sdwis.waterboards.ca.gov/PDWW/) and Massachusetts (https://www.mass.gov/service-details/public-water-supplier-document-search) to match current compliance monitoring data (where available) to the corresponding water systems and entry points sampled during UCMR 1.

~~With these updates,~~ The EPA has determined that the UCMR 1 data with these updates are the best available data collected in accordance with accepted methods regarding the

frequency and level of perchlorate nationally. The UCMR 1 data are from a census of the large water systems (serving more than 10,000 people) and a statistically representative sample of small water systems that provides the best available, national assessment of perchlorate occurrence in drinking water.

The EPA used entry point maximum measurements to estimate potential baseline occurrence and exposure at levels that exceed the potential MCLG thresholds. The maximum measurements indicate highest perchlorate levels reported in at least one quarterly sample from surface water systems and at least one semi-annual sample from ground water systems.

Table 1: Perchlorate Occurrence and Exposure (Updated UCMR 1 Data Set)

Threshold Concentration (µg/L)	Entry Points with Detections above Threshold	Water Systems with Detections above Threshold	Percent of U.S. Water Systems with Detections above Threshold	Population Served
18 µg/L	17	15	0.03 %	620,560
56 µg/L	2	2	0.004 %	32,432
90 µg/L	1	1	0.002 %	25,972

Table 1 presents the number and percentage of water systems that reported perchlorate at levels exceeding the three proposed MCLG threshold concentrations. In summary, the updated perchlorate occurrence information suggests that at an MCLG of 18 µg/L, there would be 15 systems (0.03% of all water systems in the U.S.) that would exceed the threshold, at an MCLG of 56 µg/L, two systems (0.004% of all water systems in the U.S.) would exceed the threshold,

and finally one system would exceed the MCLG threshold of 90 µg/L. Based on the analysis of drinking water occurrence presented in the 2019 proposal and the data summarized in Table 1 and the range of potential MCLGs, the EPA concludes that perchlorate does not occur ~~at~~with a frequency and at levels of public health concern in public water systems.

While the EPA has made its conclusion that perchlorate ~~occurs infrequently~~does not occur at a frequency and at levels of public health concern in public water systems based on the updated UCMR 1 data, the EPA also sought to find additional information about the perchlorate levels at the 15 water systems that had at least one reported result greater than 18 µg/L in the updated UCMR 1 data. The EPA found that perchlorate levels have been reduced at many of these water systems. Although these water systems were not required to take actions to reduce perchlorate in drinking water, many had conducted additional monitoring for perchlorate and found decreased levels or had taken mitigation efforts to address perchlorate, confirming the EPA's conclusion described above. The status of each of these systems is described in Table 2 below.

Table 2: Update on Systems with Perchlorate levels above 18 µg/L in the UCMR 1

State	System Name	Range of UCMR 1 Results (µg/L)**	Update on Mitigation and Levels of Perchlorate++
Florida	Sebring Water	ND-70	The EPA contacted the Sebring system in January 2020. Operations personnel indicated that no follow-up/updated monitoring data for perchlorate are available.

State	System Name	Range of UCMR 1 Results (µg/L)**	Update on Mitigation and Levels of Perchlorate++
Florida	Manatee County Utilities Dept	ND-30	Researchers contacted the system to identify the source of perchlorate. System personnel attributed the sole perchlorate detection under ~~UCMR1~~UCMR 1 to analytical error. System personnel indicated that three other quarterly samples collected under ~~UCMR1~~UCMR 1 as well as other subsequent perchlorate sampling efforts were non-detect. Source: AWWA (2008)
Georgia	Oconee Co.-Watkinsville	38 (single sample)	Researchers contacted the system and found that a perchlorate contaminated well was removed from service in 2003. The system indicates that perchlorate is no longer detected. Source: Luis et al. (2019)
Louisiana	St. Charles Water District 1 East Bank	ND-24	The EPA was not able to identify updated data on perchlorate levels for this system.
Maryland	City of Aberdeen	ND-19	The system's 2018 Consumer Confidence Report (CCR) indicates that perchlorate was not detected. According to the Maryland Department of Environment, perchlorate was not detected in this system in 2019. In addition, researchers contacted the system and found that there has been no detection of perchlorate since treatment was installed in 2009. Source: Luis et al. (2019)
Maryland	Chapel Hill - Aberdeen Proving Grounds	ND-20	The EPA contacted the Chapel Hill System in January 2020. Water system personnel indicate that the Chapel Hill WTP was taken off-line and was replaced with a new treatment plant and five new production wells. The new treatment plant started operations on January 27, 2020. System personnel also indicate that monitoring was conducted in November 2019 and perchlorate was not detected in either the source well water or the finished water. In

State	System Name	Range of UCMR 1 Results (µg/L)**	Update on Mitigation and Levels of Perchlorate++
			addition, according to the Maryland Department of Environment, perchlorate was not detected in this system in 2019.
Mississippi	Hilldale Water District	ND-20	The EPA contacted the Hilldale System in January 2020. Water system personnel indicated that no follow-up/updated monitoring data for perchlorate are available.
New Mexico	Deming Municipal Water System	15-20	Data from the EPA's SDWIS/FED database indicates that the entry point that reported detections in ~~UCMR~~UCMR 1 (Well #3) is now inactive (i.e., the contaminated source is no longer in use). ~~Source: SDWIS/FED (2016).~~
Nevada	City of Henderson	6-23	Researchers report that the perchlorate levels described in the system's CCR ranged from non-detect to 9.7 µg/L. Source AWWA (2008).
Ohio	Fairfield City PWS	6-27	The EPA contacted the Fairfield City System in January 2020. Water system personnel indicated that follow-up monitoring was conducted after ~~UCMR~~UCMR 1, between 2002 and 2004. The Ohio EPA provided copies of the follow-up monitoring results which indicate that results at the entry point ranged from non-detect to 13 µg/L.
Ohio	Hecla Water Association-Plant PWS	ND-32	The EPA contacted the Hecla Water Association System in January 2020. Water system personnel indicated that that no follow-up/updated monitoring data for perchlorate are available.
Oklahoma	Enid	ND-30	The EPA reviewed Oklahoma's monitoring data and did not find any monitoring results reported for perchlorate.
Pennsylvania	Meadville Area Water Authority	ND-33	The EPA contacted the Meadville System in January 2020. Water system personnel indicated that no

State	System Name	Range of UCMR 1 Results (µg/L)**	Update on Mitigation and Levels of Perchlorate++
			follow-up/updated monitoring data for perchlorate are available.
Puerto Rico	Utuado Urbano	ND-420	The EPA contacted the Puerto Rico Aqueduct and Sewer Authority (PRASA) in January 2019. PRASA personnel indicated that no updated monitoring data for perchlorate are available. *NOTE: The PRASA personnel stated that the Utuado water system was significantly impacted by hurricane Maria and monitoring records from years prior to 2017 were lost.*
Texas	City of Levelland	ND-32	Researchers found that a water storage tank was the source of perchlorate contamination, the wells feeding the tank were tested by the state and perchlorate was not detected. The water tank was shut off from service. Source: Luis et al. (2019).

** - Values have been rounded. ND describes a sampling event where perchlorate was not detected at or above the UCMR 1 minimum reporting level of 4 µg/L. UCMR 1 results collected between 2001 and 2005.

++ - To obtain updated data and/or information regarding perchlorate levels, the EPA reviewed Consumer Confidence Reports and other publicly available data, as well as published studies. In addition, the EPA contacted some water systems for information about current perchlorate levels. (USEPA, 2020b)

C. Is there a meaningful opportunity for the reduction of health risks from perchlorate for persons served by public water systems?

The ~~Agency's~~EPA's analysis presented in the 2019 proposal demonstrates that a NPDWR for perchlorate does not present a meaningful opportunity for health risk reduction for persons served by public water systems. As discussed above, the EPA found that perchlorate occurs with very low frequency at levels of public health concern. Based on updated UCMR 1

occurrence information, there were 15 water systems (0.03% of all water systems in the U.S.) that detected perchlorate in drinking water above the lowest proposed alternative MCLG of 18 µg/L and only 1 system had a detection above the proposed alternative MCLG of 90 µg/L. Specifically, Table 1 presents the population served by PWSs that were monitored under UCMR 1 for which the highest reported perchlorate concentration was greater than the identified thresholds. The EPA estimates[2] that the number of people who may be potentially consuming water containing perchlorate at levels that could exceed the levels of concern for perchlorate could range between 26,000 to and 620,000. The small number of water systems with perchlorate levels greater than identified thresholds and the corresponding small population served provides ample support for the EPA's conclusion that the regulation of perchlorate does not present a "meaningful opportunity for health risk reduction for persons served by public water systems," within the meaning of the SDWA, section 1412(b)(1)(A)(iii).

The EPA also considered the findings of the Health Risk Reduction and Cost Analysis (HRRCA, USEPA 2019c) as additional information supporting withdrawal of the regulatory determination. The HRRCA for perchlorate (which was presented in the 2019 proposal) provides a unique set of economic data indicators that are not available for regulatory determinations because the HRRCA is required for a proposed NPDWR under SDWA Section 1412(b)(3)(C),

[2] The values shown in Table 1 are based on the revised UCMR 1 data. The EPA also applied statistical sampling weights to the small systems results to extrapolate to national results. There was one small system included in the statistical sample stratum which had a perchlorate measurement exceeding 18 µg/L. Accordingly, the EPA estimates that approximately 41,000 small system customers may be exposed to perchlorate greater than 18 µg/L.

but is not ~~prepared~~required to support a regulatory determination. ~~Perchlorate is a unique contaminant for which~~Accordingly, because the ~~Agency has done significant new analysis not undertaken for~~EPA initially determined that perchlorate met the criteria for regulation and began the regulatory ~~determinations. Accordingly~~ analysis process, the HRRCA was available with respect to perchlorate, and the Agency considered this comprehensive economic analysis in informing its decision to withdraw the regulatory determination.

Specifically, the HRRCA provides a description of the potential ~~quantifiable and non-quantifiable~~ benefits and costs of a drinking water regulation for perchlorate. For all potential regulatory levels considered for perchlorate (18, 56, and 90 µg/L) the total costs associated with establishing a regulation were substantially higher than the potential range of ~~quantifiable~~ benefits. The infrequent occurrence of perchlorate at levels of health concern imposes high monitoring and administrative cost burdens on public water systems and the states, while having little impact on health risk reductions and the associated low estimates of benefits.

Based on a comparison of costs and benefits estimated at the three potential regulatory levels, the EPA determined in the 2019 proposal that the benefits of establishing a drinking water regulation for perchlorate do not justify the potential costs.

A drinking water regulation for perchlorate would impose significant burden on states and water systems, mainly associated with requirements for monitoring but which would result in very few systems having to take action to reduce perchlorate levels. It is of paramount importance that water systems (particularly medium, small and economically distressed systems)

focus their limited resources on actions that ensure compliance with existing NPDWRNPDWRs and ~~sustain~~maintain their technical, managerial, and financial capacity ~~maintain~~ to improve system operations and the quality of water being provided to their customers rather than spending resources monitoring for contaminants that are unlikely to occur.

D. What is the EPA's final regulatory determination on perchlorate?

Based on the EPA's ~~new~~ analysis of the best available public health information, and after careful review and consideration of public comments on the June 2019 proposal, the Agency is withdrawing its 2011 determination and is ~~now~~ making a final determination to not ~~to~~ regulate perchlorate. Accordingly, the EPA will not issue a NPDWR for perchlorate at this time. While the EPA has found that perchlorate may have an adverse effect on human health, based on the analysis presented in this notice and supporting record, the EPA has determined that perchlorate does not occur in public water systems ~~at~~with a frequency and at levels of public health concern and that regulation of perchlorate does not present a meaningful opportunity to reduce health risks for persons served by public water systems. This conclusion is based on the best available peer reviewed science and data collected in accordance with accepted methods on perchlorate health effects and occurrence.

Commented [BC3]: Why was this added? I recommend not having it there – but am interesting in knowing if OGC advised this change.

Commented [BE4R3]: Yes this edit was recommended by OGC to be clear we could reconsider if the data changes.

IV. Summary of Key Public Comments on Perchlorate

The EPA received approximately 1,500 comments from individuals or organizations on the June 2019 proposal. This section briefly discusses the key technical issues raised by commenters and the EPA's response. Comments are also addressed in the ''Comment Response

Document for the Final Regulatory Action for Perchlorate'' (USEPA, 2020a) available at http://www.regulations.gov (Docket ID No. EPA–HQ–OW–2018–0780).

A. SDWA Statutory Requirements and the EPA's Authority

The EPA received comments stating the Agency should promulgate an MCLG and MCL for perchlorate and comments stating the Agency should not promulgate a regulation. After considering these comments the ~~Agency~~EPA has re-evaluated perchlorate in accordance with the SDWA, section 1412~~(b)~~(1)(A), which requires that the ~~EPA~~Agency promulgate a NPDWR if (i) the contaminant may have an adverse effect on the health of persons; (ii) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and (iii) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The ~~Agency~~EPA has determined, based upon the best available peer reviewed science and data collected in accordance with accepted methods, that perchlorate does not occur ~~with~~at a frequency and at levels of public health concern, and ~~there is not~~that regulation of perchlorate does not present a meaningful opportunity for health risk reduction. ~~Therefore,~~Because perchlorate does not meet the ~~Agency has determined not~~ statutory criteria for regulation, the EPA lacks the authority to ~~promulgate~~issue a MCLG or NPDWR for perchlorate~~.~~, and is therefore withdrawing its 2011 regulatory determination and issuing

this final determination to not regulate perchlorate. For more information regarding EPA's statutory authority to withdraw its regulatory determination, see Section II C above.

B. *Health Effects Assessment*

Health Effects/MCLG Derivation

The ~~Agency~~EPA received comments indicating that the ~~EPA~~Agency should utilize different approaches to derive the MCLG for perchlorate including approaches that some states used to develop their perchlorate advisory levels or drinking water standards. The ~~Agency~~EPA considered a number of alternative approaches to develop the MCLG for perchlorate and in accordance with the SDWA, section 1412(e)), the Agency sought recommendations from the Science Advisory Board. The EPA derived the proposed MCLG for perchlorate based on the approach recommended by the Science Advisory Board (SAB) (SAB for the U.S. EPA, 2013). The SAB recommended that *"the EPA derive a perchlorate MCLG that addresses sensitive life stages through physiologically-based pharmacokinetic/pharmacodynamic modeling based upon its mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters."* The EPA has implemented these recommendations and has obtained two independent peer reviews of the analysis. These peer reviewers stated that: "*Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models,*

with limited additional work to address the committee's comments below, the current models are fit-for-purpose to determine an MCLG" (External Peer Reviewers ~~for USEPA~~for USEPA, 2018, p. 2).

The EPA received comments indicating the most sensitive life stages were not selected and/or considered in the Agency's approach. The EPA disagrees. Gestational exposure to perchlorate during neurodevelopment is the most sensitive time period. The NRC concluded that the population most sensitive ~~population~~ to perchlorate exposure are "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mn5hjprkt","properties":{"formattedCitation":"(National Research Council (NRC), 2005b)","plainCitation":"(National Research Council (NRC), 2005b)","noteIndex":0},"citationItems":[{"id":350,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":350,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"National Research Council (NRC)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. In addition, there is clear evidence that disrupted maternal thyroid hormone levels during gestation can impact neurodevelopment later in life (Alexander et al., 2017; Costeira et al., 2011; Endendijk et al., 2017; Ghassabian,

Bongers-Schokking, Henrichs, Jaddoe, & Visser, 2011; Glinoer & Delange, 2000; Glinoer & Rovet, 2009; Gyllenberg et al., 2016; Henrichs et al., 2010; Korevaar et al., 2016; Morreale de Escobar, Obregón, & Escobar del Rey, 2004; Noten et al., 2015; Pop et al., 2003, 1999; SAB for the U.S. EPA, 2013; Thompson et al., 2018; van Mil et al., 2012; Wang et al., 2016; Zoeller & Rovet, 2004; Zoeller et al., 2007). ~~The EPA's analysis concludes that~~ The available data demonstrate that the fetus of the first trimester pregnant mother, when compared to other life-stages, experiences the greatest impact from ~~equivalent doses~~the same dose of perchlorate ~~exposure~~, which is described in detail in Section 6 of the document "Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water" (USEPA, 2019a). ~~In addition, the EPA disagrees~~Some commenters suggested that the bottle-fed ~~infants are the most~~infant is a more sensitive ~~population~~ life-stage. The EPA disagrees as described in the January 2017 Peer Review Report on the original Biologically Based Dose Response (BBDR) model, the bottle-fed infant's thyroid hormone levels were not impacted by doses of perchlorate up to 20 µg/day (External Peer Reviewers for USEPA, 2017). This lack of any impact is due primarily to the iodine in the formula, which offsets the impact of perchlorate on the thyroid.

The ~~Agency~~EPA received comments advocating for the use of a~~the~~ population-based approach~~,~~ evaluating the shift in the proportion of a population that would fall below a hypothyroxinemic cut point under a perchlorate exposure scenario. The ~~Agency~~EPA chose to develop the MCLG using dose-response functions from the epidemiological literature to

estimate neurodevelopmental impacts in the offspring of pregnant women exposed to perchlorate. The EPA selected this proposed approach because it is consistent with the SDWA's definition of a MCLG to avoid adverse health effects and because it is most consistent with the SAB recommendations. In addition, the fact that thyroid hormone levels vary by reference population and that there is not a defined value representing hypothyroxinemia makes the population-based approach less desirable than the approach selected (USEPA, ~~2018b~~2018).

End Point Selection/Basis

The ~~Agency~~EPA received comments regarding the magnitude of an IQ change which should be used in ~~considering~~deriving the MCLG. ~~Many comments stated that the Agency should at most consider a 1% IQ change. However, several commenters stated a 3% change is too small to have a meaningful impact and suggested the Agency consider a higher IQ percent change.~~ The ~~Agency's~~EPA's proposed MCLG was based upon avoiding a 2% change in IQ in the most sensitive life stage and the EPA also requested comment on alternative options for the MCLG that would respectively avoid 1% or 3% change in IQ in the most sensitive ~~lifestage~~life stage. Many comments stated that the EPA should at most consider a 1% IQ change. However, several commenters stated a 3% change is too small to have a meaningful impact and suggested the EPA consider a higher IQ percent change.

The EPA uses a variety of science policy approaches to select points of departure for developing regulatory values. For instance, in noncancer risk assessment the EPA often uses

a percentage change in value. When assessing toxicological data, a 10 ~~percent~~% extra risk (for discrete data), or a 1 standard deviation (i.e., 15 IQ points) change from the mean (for continuous data) is often used (USEPA, 2012). A smaller response to inform a POD has been applied when using epidemiological literature because there is an inherently more direct relationship between the study results and the exposure context and health endpoint.

Commented [BC5]: Can you send me the source for this and the page number? Thanks.

Commented [BE6R5]: See page 21 [HYPERLINK "https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf"]
Also note this text was in the perchlorate proposal near the bottom of page 30356 [HYPERLINK "https://www.federalregister.gov/documents/2019/06/26/2019-12773/national-primary-drinking-water-regulations-perchlorate"]

Given the difficulty in identifying a response below which no adverse impact occurs when considering a continuous outcome in the human population, the EPA looked to its Benchmark Dose Guidance (2012) for insight regarding a starting point. Specifically, ''[a] BMR of 1% has typically been used for quantal human data from epidemiology studies'' (p. 21, USEPA, 2012). For the specific context of setting an MCLG for perchlorate, the EPA ~~made a policy decision to evaluate~~evaluated the level of perchlorate in water associated with a 1 ~~percent~~% decrease, a 2 ~~percent~~% decrease, and a 3 percent decrease in the mean population IQ (i.e., 1, 2 and 3 IQ points).

In evaluating the frequency and level of occurrence of perchlorate in drinking water the ~~Agency~~EPA has found that perchlorate does not occur with frequency even at the lowest alternative MCLG of 18 µg/L which is based upon avoiding a 1% change in IQ in the most sensitive ~~lifestage~~life stage.

The ~~Agency~~EPA received comments that the proposed MCLG did not incorporate an adequate margin of safety to comply with the SDWA. The ~~Agency~~EPA disagrees that ~~there was a failure~~it failed to use an adequate margin of safety. The ~~Agency's~~EPA's assessment

focused upon the most sensitive subset of the population, specifically offspring whose mothers had low (75 µg/day) iodine intake and were ~~hypothyroxinemic~~hypothyroxinemic (fT4 in the lowest 10th percentile of the population). In addition, to account for uncertainties and to ensure the most sensitive subset of the population is protected ~~within~~with an adequate margin of safety, a 3-fold uncertainty factor was applied to the proposed MCLG calculation (USEPA, 2019a). More discussion on the uncertainty factor is presented in the section "Consideration of Uncertainties."

The EPA received some comments stating ~~that~~ the selection of the study for informing the relationship between maternal hormone levels (fT4) and IQ was inadequately described. Other comments ~~support~~supported the ~~Agency's~~EPA's study selection. The EPA concludes that selection of the Korevaar et al. (2016) study is appropriate because that study provides the most robust data available with a clear measure of neurodevelopment that can be expressed as a function of changing maternal fT4 exposure, which is necessary to the development of the model.

BBDR and PBPK Models

The ~~Agency~~EPA received comments indicating the BBDR model was not transparent, scientifically valid, or based on robust data. The ~~Agency~~EPA disagrees. The model represents the best available peer reviewed science and ~~utilizes~~uses the best available data to inform a MCLG for perchlorate. The EPA does not believe there is a significant lack of transparency with respect to the assumptions related to the BBDR model. Appendix A of

the EPA's Proposed MCLG Approaches report outlines the justification for all assumptions used in the development of the BBDR model (USEPA, 2019a). The EPA also disagrees with the assertion the BBDR model is far too uncertain to be relied upon as the basis for the derivation of the RfD. The EPA has used the best available science to calibrate the pharmacokinetic aspects of the BBDR model. The development of the BBDR model was ~~performed~~ in response to SAB recommendations and a model was deemed to be a more ~~superior~~refined approach to estimating a dose-response relationship between perchlorate exposure and maternal fT4 than anything that was available in the current scientific literature. The EPA disputes the claim that there are issues with the scientific validity of the BBDR model as the Agency conducted a peer review of the approach proposed and the reviewers stated the approach was "fit for purpose" to inform a MCLG for perchlorate (External Peer Reviewers for U.S. EPA, 2018, p. 2).

Consideration of Uncertainties

The ~~Agency~~EPA received comments on the ~~EPA's~~Agency's use of Uncertainty Factors (UFs~~).~~; with most commenters ~~suggested~~suggesting that the EPA should consider a higher UF. The ~~Agency~~EPA thoroughly considered the application of UFs when deriving the RfDs and followed guidance presented in "A review of the reference dose and reference concentration processes" (USEPA, 2002). The ~~Agency believes~~EPA concluded that the UFs are adequately justified and subsequently no changes have been made. Justification for each

of the UFs described in this comment can be found in Section 11 of the Agency's MCLG Derivation report (USEPA, 2019a).

The AgencyEPA selected a UF of 3 for inter-individual variability because the Agency specifically modeled groups within the population that are identified as likely to be at greater risk toof the adverse effects from perchlorate in drinking water (i.e., the fetus of the iodide deficient pregnant mother). The AgencyEPA selected model parameters to account for the most sensitive individuals in that group (i.e., muted TSH feedback, low fT4 values, low-iodine intake). As discussed in the MCLG Derivation report, the EPA has attempted to select the most appropriate inputs to protect the most sensitive population with an adequate margin of safety (USEPA, 2019a). The AgencyEPA has determined that the selection of a UF of 3 for inter-individual variability is justified. As described in the MCLG Derivation report, because the output from the BBDR model is specific to the sensitive population and therefore the Agency has made no change inthe EPA concluded that the UF of 3 is appropriate. In regards to variation in sensitivity among the members of the human population (i.e., inter-individual variability), section 4.4.5.3 of the EPA guidance "A review of the reference dose and reference concentration process" (USEPA, 2002) document states, "In general, the Technical Panel reaffirms the importance of this UF, recommending that reduction of the intraspecies UF from a default of 10 be considered only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s). Similar to the interspecies UF, the intraspecies UF can be considered to consist of both a toxicokinetic and

toxicodynamic portion (i.e. 10^0.5 each)" (USEPA, 2002). Given that the BBDR model significantly accounts for differences within the human population, the full UF of 10 is not warranted.

One commenter suggested using a UF greater than 1 to account for ~~LOAEL-to-NOAEL~~the extrapolation~~.~~ of the lowest-observed adverse effect level (LOAEL) to the no-observed-adverse-effect-level (NOAEL). LOAELs and NOAELs were not identified or used by the EPA in its assessment because the Agency ~~has determined that the IQ~~ employed a sophisticated BBDR modeling approach, which was coupled with extrapolation to changes ~~presented as options in the 2019 proposal~~in IQ using linear regression, to determine a POD that would not be expected to represent ~~NOAELs~~ an adverse effect. Therefore, ~~including~~ a UF ~~to account for extrapolating from a LOAEL to a NOAEL~~ of 1 is ~~not needed. Additional~~appropriate. Other commenters suggested incorporating UFs for database deficiencies. Based on the findings of the NRC report, the EPA has previously concluded that this UF was not needed for deficiencies in the perchlorate database (NRC, 2005; USEPA, 2005a). The EPA believes that a UF of 1 to account for database deficiencies is still appropriate given that the state of the perchlorate database has only increased since 2005.

C. *Occurrence Analysis*

The EPA received comments suggesting that the revised UCMR 1 data did not provide an adequate estimate ~~about~~of the perchlorate occurrence in drinking water systems. Some commenters indicated that the age of the collected data rendered the occurrence

analysis obsolete and overestimated, since it no longer captures current lower contamination conditions ~~which~~that have been achieved due to mitigation measures taken in the Colorado River Basin. Other commenters criticized ~~the~~ EPA for replacing UCMR 1 data with compliance data for the States of California and Massachusetts.

The EPA recognizes that changes in perchlorate levels (increasing or decreasing) may have occurred in water systems since the UCMR 1 samples were collected between 2001 to 2005. The ~~Agency~~EPA updated the UCMR 1 data set to improve its accuracy in representing the current conditions for states that have enacted perchlorate regulations since the UCMR 1 monitoring was conducted. As outlined in the June 26, 2019 proposal, the EPA updated occurrence data for California and Massachusetts with current compliance data as reported by the states. Systems from these two states that were sampled during the UCMR 1 and that had reported perchlorate detections were updated with more recently measured values taken from current compliance monitoring data from Consumer Confidence Reports and state-level perchlorate compliance monitoring data to match corresponding water systems and entry points ~~between the two sources~~.

The EPA has determined that the updated UCMR 1 ~~data~~ are the best available data collected in accordance with accepted methods on the frequency and level of perchlorate occurrence in drinking water on a national scale.

V. Conclusion

With this withdrawal of the 2011 perchlorate regulatory determination and final determination to not to regulate perchlorate, the EPA announces that there will be no NPDWR for perchlorate at this time. The EPA could consider re-listing perchlorate on the CCL and could proceed to regulation in the future if the occurrence or health risk information changes. As with other unregulated contaminants, the EPA could address thewill consider addressing limited instances of elevated levels of perchlorate by working with the affected system and state, as appropriate.

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List of Subjects in 40 CFR Parts 141 and 142

Administrative practice and procedure, Chemicals, Indians-lands, Intergovernmental relations, Radiation protection, Reporting and recordkeeping requirements, Water supply.

Dated:_____

_____

Andrew ~~R.~~ Wheeler,

Administrator.

DELIBERATIVE DRAFT
TO BE UPDATED FOLLOWING INTER AGENCY REVIEW

MEMORANDUM

SUBJECT: Notice of Final Action on Perchlorate
(Tier 1 Action; SAN 5555; RIN 2040-AF28) – **ACTION MEMORANDUM**

FROM: David P. Ross
Assistant Administrator (4101M)

THRU: Office of Policy (1803A)
Office of Executive Secretariat (1105A)

TO: Andrew J. Wheeler
Administrator (1101A)

PURPOSE
Attached for your signature is the action titled "Notice of Final Action on Perchlorate."

On February 11, 2011, the EPA published a determination to regulate perchlorate in drinking water (76 FR 7762). On June 26, 2019 (84 FR 30524), the EPA published the proposed National Primary Drinking Water Regulation (NPDWR) for Perchlorate and requested public comments on multiple alternative actions, including withdrawing the Agency's 2011 determination to regulate perchlorate. The EPA received approximately 1,500 comments on the proposed rule.

In this notice, the EPA is withdrawing the 2011 Regulatory Determination and is making a final determination not to regulate perchlorate based on the Agency's consideration of public comments and the best available information.

DEADLINE/TIMELINE
Section 1412(b)(1)(A) of the Safe Drinking Water Act (SDWA) requires the EPA to issue a proposed NPDWR within 24 months of the final regulatory determination and a final NPDWR within 18 months after the proposal. However, when the EPA consulted with the Science Advisory Board (SAB) regarding a planned methodology for deriving the maximum contaminant level goal (MCLG) for perchlorate, the Agency received recommendations to develop a physiologically based pharmacokinetic model (i.e., a biologically based dose-response model (BBDR)) to predict the effects of perchlorate exposure on thyroid function in pregnant women and their children, instead. The EPA collaborated with Food and Drug Administration scientists to perform the modeling recommended by the SAB and completed the analysis and associated peer reviews in March 2018. This delayed the EPA in proposing a NPDWR within 24 months.

In February 2016, the Natural Resources Defense Council (NRDC) filed a lawsuit for failure of

the EPA to perform its mandatory duties of proposing and finalizing a regulation for perchlorate in accordance with timelines provided in the SDWA. On October 18, 2016, the U.S. District Court for the Southern District of New York entered a Consent Decree, requiring the EPA to sign for publication a proposal for a MCLG and NPDWR for perchlorate in drinking water no later than October 31, 2018, and to sign for publication a final MCLG and NPDWR for perchlorate in drinking water no later than December 19, 2019. The Court later extended the deadline for the EPA to propose a MCLG and NPDWR for perchlorate in drinking water to May 28, 2019, and extended the date for signature of a final MCLG and NPDWR no later than June 19, 2020.

In compliance with the deadline established in the Consent Decree, on May 23, 2019, the Administrator signed a proposed rulemaking notice seeking public comment on a range of options regarding the regulation of perchlorate in public drinking water systems. The EPA published the proposed rule in the *Federal Register* on June 26, 2019. The public comment period for the proposal ended on August 26, 2019, and the EPA received approximately 1,500 comments.

DESCRIPTION of the ATION

Perchlorate is an inorganic anion that occurs naturally. It is also manufactured as an oxidizer for rockets, missiles, and fireworks and can be an impurity in hypochlorite disinfectants. The public may be exposed to perchlorate through food and drinking water. At certain levels, perchlorate can prevent the thyroid gland from getting enough iodine, which can affect thyroid hormone production. For pregnant women with low iodine levels, sufficient changes in thyroid hormone levels may cause changes in the child's brain development. For infants, changes to thyroid hormone function can also impact brain development.

The SDWA sets forth three criteria that must be met for the EPA to issue a MCLG and promulgate a NPDWR. Specifically, the EPA must determine that (1) "the contaminant may have an adverse effect on the health of persons;" (2) "the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern;" and (3) "in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems" (SDWA 1412(b)(1)(A)).

In the attached notice, the EPA concludes that, based on new data and the Agency's analysis since the issuance of the 2011 Regulatory Determination, perchlorate does not in fact meet the statutorily prescribed criteria for regulation. The new data and analysis indicate that perchlorate does not occur in public water systems with a frequency and at levels of public health concern. Specifically, the new peer-reviewed health effects analysis resulted in the health based proposed MCLG and proposed alternative MCLGs for perchlorate that are higher concentrations in drinking water (18 – 90 µg/L) than the concentrations that the EPA considered to be levels of public health concern in the Agency's analysis for the determination to regulate in 2011 (1-47 µg/L). In addition, the updated occurrence analysis shows that the frequency of occurrence of perchlorate in public water systems at levels exceeding any of the alternative proposed MCLGs (0.38% - 0.02%) is significantly lower than the frequency considered in the EPA's analysis for the 2011 Regulatory Determination (4% - 0.39%). Based on this information, the

EPA is announcing the Agency's conclusion that perchlorate does not occur in public water systems "with a frequency…of public health concern" and, therefore, regulation of perchlorate does not present a "meaningful opportunity for health risk reduction for persons served by public water systems" as required for regulation under the SDWA. Accordingly, perchlorate no longer meets the statutory criteria for regulation because the EPA does not have the authority to issue a MCLG or promulgate a NPDWR for perchlorate.

Therefore, the EPA is not issuing a final MCLG or NPDWR for perchlorate. ~~However, the EPA maintains the authority to re-list perchlorate on future Contaminant Candidate Lists and proceed with regulating perchlorate in the future if occurrence or risk information changes.~~ The EPA will consider addressing limited instances of elevated levels of perchlorate by working with the affected system and state, as appropriate.

Commented [BC1]: Is this statement in the final action? Why are we including it here?

Commented [BE2R1]: There is similar language in conclusion section However it is not necessary to include in the Action memo

STAKEHOLDER INVOLVEMENT and ANTICIPATED RESPONSE

The EPA considered the approximately 1,500 comments that were submitted on the proposed regulation. The EPA also consulted with the National Drinking Water Advisory regarding the proposed regulation. The EPA expects a variety of reactions and responses from stakeholders. The NRDC will likely sue the EPA for failure to comply with the Consent Decree and will likely challenge the Agency's authority to withdraw a Regulatory Determination. Officials from the States of California and Massachusetts, public health groups and environmental groups will likely state that a low perchlorate maximum contaminant level is needed to protect children's health. Industry groups, including the American Water Works Association, the Perchlorate Study Group, the American Chemistry Council, and the U.S. Chamber of Commerce will support the decision not to regulate perchlorate in drinking water. These groups will agree with the EPA's determinations that perchlorate does not occur frequently at levels of public health concern and there is not a meaningful opportunity for health risk reduction for persons served by public water systems.

INTERNAL DEVELOPMENT and REVIEW PROCESS

The attached notice reflects the direction provided by the Administrator in the Options Selection meetings held on January 9 and March 18, 2020. The Office of Water (OW) convened a Final Agency Review meeting for this action on May 7, 2020. The following offices concurred without comment: the Office of Research and Development, the Office of Land and Emergency Management, the Office of Air and Radiation, and the Office of Chemical Safety and Pollution Prevention. The following offices concurred with comment: the Office of General Counsel (OGC), the Office of Policy (OP), and the Office of Children's Health Protection (OCHP). The OW has incorporated revisions identified in the comments from the OGC. The OW has also incorporated most of the suggested revisions identified by the OP, the key exception being that we are not incorporating OP's recommendation to not list the cost benefit analysis as a factor in the decision to withdraw the regulatory determination. The OW has worked with OGC to incorporate language that clarifies that this does not set a precedent for future regulatory determinations. The OW is not incorporating the majority of recommendations made by the OCHP, which address the health effects and occurrence analysis and are issues we have evaluated previously, including in response to OCHP's input on the proposal and in response to public comments.

DELIBERATIVE DRAFT
TO BE UPDATED FOLLOWING INTER AGENCY REVIEW

INTERAGENCY REVIEW
The Office of Management and Budget initiated review of the *Federal Register* notice: "Notice of Final Action on Perchlorate" on [date placeholder].

PEER REVIEW
For the proposed rulemaking, the OW followed the EPA's Peer Review Handbook and Agency policy titled "Conflicts of Interest Review Process for Contractor-Managed Peer Reviews of EPA HISA and ISI Documents" when conducting the peer review of models used to derive the proposed MCLGs for perchlorate. The EPA convened an independent peer review panel to evaluate the BBDR models in 2017 and a second, expert peer review panel in 2018 to evaluate the update of the BBDR model and approaches to link the BBDR model output to neurodevelopment endpoints in epidemiology studies to derive an MCLG. The EPA also sought input from the SAB, as required by the SDWA, prior to developing the proposed MCLGs.

RECOMMENDATION
I recommend that you sign the attached *Federal Register* notice titled "Notice of Final Action on Perchlorate."

Attachments (2)

Message

From: Miller, Wynne [Miller.Wynne@epa.gov]
Sent: 2/6/2019 2:06:37 PM
To: Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Beck, Nancy [Beck.Nancy@epa.gov]; Morris, Jeff [Morris.Jeff@epa.gov]
CC: Keigwin, Richard [Keigwin.Richard@epa.gov]; Messina, Edward [Messina.Edward@epa.gov]; Dunn, Alexandra [dunn.alexandra@epa.gov]; Baptist, Erik [Baptist.Erik@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]
Subject: FW: Technical Support Documents - Draft Perchlorate Rule Proposal
Attachments: 181129_DRAFT MCLG TSD.DOCX; Draft Perchlorate HRRCA 2019-02-03.docx; PerchlorateOccMonitoringReport_Updated 2-1-19.docx; Perchlorate T&C November 2018.docx; Perchlorate BAT and SSCT November 2018.docx; WA459_T4_Vol1 Main Report_181113.docx

Per my previous note … here's the second email with the support documents for perchlorate.

From: Hernandez-Quinones, Samuel
Sent: Monday, February 04, 2019 3:55 PM
To: Johnson, Ann <Johnson.Ann@epa.gov>; Dockins, Chris <Dockins.Chris@epa.gov>; Shao, Nicole <Shao.Nicole@epa.gov>; Miller, Gregory <Miller.Gregory@epa.gov>; Flowers, Lynn <Flowers.Lynn@epa.gov>; Foster, Stiven <Foster.Stiven@epa.gov>; Kyprianou, Rose <Kyprianou.Rose@epa.gov>; Miller, Wynne <Miller.Wynne@epa.gov>; Raffaele, Kathleen <raffaele.kathleen@epa.gov>
Cc: Christ, Lisa <Christ.Lisa@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Technical Support Documents - Draft Perchlorate Rule Proposal

Preliminary draft for internal EPA review

Hi,

Attached are copies of the draft technical support documents that were used as basis for the Perchlorate Rule Proposal. As mentioned earlier today we are not requesting comments on these documents within the two-week review time frame.

Economic Analysis
MCLG Derivation Document
Treatment Technologies & Costs Document
Occurrence & Monitoring Report
MCLG Approaches Document
Best Available Technologies Document

Thanks
Sam

==========

Samuel Hernández Quiñones, P.E.
Environmental Engineer
Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

From: Hernandez-Quinones, Samuel
Sent: Monday, February 04, 2019 10:32 AM

To: Cc: Christ, Lisa <christ.lisa@epa.gov>; Burneson, Eric <burneson.eric@epa.gov>; Flaharty, Stephanie <Flaharty.Stephanie@epa.gov>; Messier, Dawn <Messier.Dawn@epa.gov>; Wehling, Carrie <Wehling.Carrie@epa.gov>; Huff, Lisa <Huff.Lisa@epa.gov>; Khera, Rajiv <Khera.Rajiv@epa.gov>
Subject: Request for review - Draft Perchlorate Rule Proposal

Preliminary draft for internal EPA review

Hi,

Attached for your review is the Draft Perchlorate Rule Proposal (Preamble and Regulatory Text). As discussed previously we are asking that you provide your questions and or comments on the draft document to me by COB 2/15/2019. In order to keep with the consent decree deadline, we need to complete this step of the process within two weeks, if there are any issues that require technical discussions please let me know so that we can arrange any necessary working meeting.

I will follow-up with another email later today that contains the draft version of the technical support documents that were used as the basis for the Perchlorate proposal. Since those are very lengthy documents we are not requesting that you submit input and/or comments on those within the two- week time frame.

Please let me know if you have any questions.

Thanks
Sam
==========
Samuel Hernández Quiñones, P.E.
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Office of Water
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460
202-564-1735

"USEPA Protecting Human Health and the Environment"

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Environmental Protection
Agency

DRAFT Technical Support Document: Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water

NOTICE

This document is a **review draft.** It has not been formally disseminated by the EPA. It does not represent and should not be construed to represent any Agency determination or policy. It is being circulated for public comment only.

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List of Tables

[TOC \h \z \c "Table"]

List of Figures

[TOC \h \z \c "Figure"]

Abbreviations and Acronyms

Agency	U.S. Environmental Protection Agency
Approaches Report	*Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water*
ATA	American Thyroid Association
BBDR	biologically based dose-response
BW	bodyweight
CalEPA	California Environmental Protection Agency
CBCL	Child Behavior Checklist
CCL	Contaminant Candidate List
CI	confidence interval
CSFII	Continuing Survey of Food Intakes by Individuals
DWI	drinking water ingestion
EFH	Exposure Factors Handbook
EPA	U.S. Environmental Protection Agency
FDA	Food and Drug Administration
fT4	free thyroxine
GW	gestational week
HPT	hypothalamic-pituitary-thyroid
HRL	Health Reference Level
IQ	intelligence quotient
IRIS	Integrated Risk Information System
LOAEL	lowest-observed adverse effect level
LOD	level of detection
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MDI	Mental Developmental Index
NAAQS	National Ambient Air Quality Standards
NHANES	National Health and Nutrition Examination Survey
NIS	sodium-iodide symporter
NOAEL	no observed adverse effect level
NOAL	no observed effect level
NPDWR	National Primary Drinking Water Regulation
NRC	National Research Council
OHAT	Office of Health Assessment and Translation
PBPK	physiologically based pharmacokinetic

PD	pharmacodynamic
PDI	Psychomotor Development Index
POD	point of departure
RfD	reference dose
ROB	Risk of Bias
RSC	relative source contribution
SAB	Science Advisory Board
SD	standard deviation
SDWA	Safe Drinking Water Act
T3	triiodothyronine
T4	thyroxine
TDS	Total Diet Study
THOP	transient hypothyroxinemia of prematurity
TSH	thyroid stimulating hormone
UF	uncertainty factor
UF_A	Uncertainty factor, animal-to-human
UF_D	Uncertainty factor, database deficiency
UF_H	Uncertainty factor, within-human variability
UF_L	Uncertainty factor, LOAEL-to-NOAEL
UF_S	Uncertainty factor, subchronic-to-chronic
WHO	World Health Organization
WWEIA	What We Eat in America

Acknowledgements

This document was prepared by the Environmental Protection Agency, Office of Ground Water and Drinking Water. Abt Associates Inc. provided assistance in performing the analyses detailed in this document.

1. Introduction

The purpose of this document is to provide the U.S. Environmental Protection Agency's (EPA or the Agency) justification for the selected approach to inform the Maximum Contaminant Level Goal (MCLG) for perchlorate in drinking water. MCLGs are non-enforceable, health-based goals that the EPA sets for each regulated drinking water contaminant. In accordance with the Safe Drinking Water Act (SDWA), the EPA sets MCLGs at a level at which no known or anticipated adverse effects on the health of persons occur, and which allows an adequate margin of safety. SDWA requires that the EPA use the best available, peer reviewed science and supporting studies conducted in accordance with accepted practices; and data collected by accepted methods or best available methods. The process of setting an MCLG considers only public health, and the limits of analytical measurement and treatment technology effectiveness are not taken into account. The SDWA requires that the EPA establish the enforceable Maximum Contaminant Level (MCL) as close as feasible to the MCLG, taking costs into consideration. SDWA also requires that the EPA prepare a Health Risk Reduction Cost Analysis that includes an estimate of the costs, benefits, and an assessment of effects of the contaminant on the general population and on groups within the population such as infants, pregnant women, the elderly or other subpopulations that are likely to be at greater risk of adverse health effects.

The perchlorate MCLG will be based on analyses presented in the peer-reviewed report, *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (hereafter referred to as the "Approaches Report") [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2018</Year><RecNum>1995</RecNum><DisplayText>(U.S. EPA, 2018)</DisplayText><record><rec-number>1995</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1527619441">1995</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Proposed approaches to inform the derivation of a maximum contaminant level goal for perchlorate in drinking water</title></titles><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]. The Approaches Report presents a Biologically Based Dose Response (BBDR) model that predicts thyroid hormone changes that may result from perchlorate exposure in pregnant women. The Approaches Report also describes the EPA's analysis of epidemiologic studies that allow for a connection between the thyroid hormone changes in pregnant women predicted by the BBDR model and neurodevelopmental effects in their offspring.

1.1 Evaluation of Perchlorate under the Safe Drinking Water Act

The EPA included perchlorate on the first three iterations of the Contaminant Candidate List (CCL), starting in 1998, after data collection and requests for comments. The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to the EPA drinking water regulations. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA uses the CCL to identify priority contaminants for regulatory decision-making and information collection.

In 2005, at the request of the EPA and other federal agencies, the National Research Council (NRC) evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure

could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>]. A significant inhibition of iodide uptake results in intra-thyroid iodide deficiency, decreased synthesis of key thyroid hormones (triiodothyronine (T3) and thyroxine (T4)), and increased thyroid stimulating hormone (TSH). The NRC also concluded that a prolonged decrease of thyroid hormones is potentially more likely to have adverse effects in sensitive populations (e.g., people with thyroid disorders, pregnant women, fetuses, and infants). Based on NRC's recommendations, the EPA adopted a reference dose (RfD) of 0.7 µg/kg/day in 2005 [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2005</Year><RecNum>295</RecNum><DisplayText>(U.S. EPA, 2005a)</DisplayText><record><rec-number>295</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1470935048">295</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA, </author></authors><secondary-authors><author>National Center for Environmental Assessment</author></secondary-authors></contributors><titles><title>Integrated Risk Information System chemical assessment summary: Perchlorate and perchlorate salts</title></titles><dates><year>2005</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/1007_summary.pdf</style><style face="normal" font="default" size="100%"> </style></url></related-urls></urls></record></Cite></EndNote>]. This value was based on a no observed effect level (NOEL; 7 µg/kg/day) identified by a study [ADDIN EN.CITE <EndNote><Cite><Author>Greer</Author><Year>2002</Year><RecNum>204</RecNum><DisplayText>(Greer, Goodman, Pleus, & Greer, 2002)</DisplayText><record><rec-number>204</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1467812686">204</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Greer, M.A.</author><author>Goodman, G.</author><author>Pleus, R.C.</author><author>Greer, S.E.</author></authors></contributors><titles><title>Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>927</pages><volume>110</volume><number>9</number><dates><year>2002</year></dates><urls></urls></record></Cite><Cite><Author>Greer</Author><Year>2002</Year><RecNum>204</RecNum><record><rec-number>204</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1467812686">204</key></foreign-

keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Greer, M.A.</author><author>Goodman, G.</author><author>Pleus, R.C.</author><author>Greer, S.E.</author></authors></contributors><titles><title>Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>927</pages><volume>110</volume><number>9</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] in healthy adults for the inhibition of radioactive iodide uptake and the application of an uncertainty factor of 10 for intraspecies variability.

In October 2008, the EPA published a preliminary determination not to regulate perchlorate in drinking water using a Health Reference Level (HRL) of 15 µg/L, which was derived from the RfD of 0.7 µg/kg/day, using a default bodyweight of 70 kg, a default drinking water consumption rate of 2 L/day, and a perchlorate-specific relative source contribution (RSC) of 62 percent for a pregnant woman [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2008</Year><RecNum>121</RecNum><DisplayText>(U.S. EPA, 2008a)</DisplayText><record><rec-number>121</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465916938">121</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Interim drinking water health advisory for perchlorate</title></titles><dates><year>2008</year></dates><pub-location>Washington, D.C.</pub-location><isbn>EPA 822-R-08-025</isbn><urls><related-urls><url><style face="underline" font="default" size="100%">https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1004X7Q.TXT</style></url></related-urls></urls></record></Cite></EndNote>]. The RSC is the percentage of the RfD remaining for drinking water after other sources of exposure to perchlorate (e.g., food) have been considered. In December 2008, the EPA issued an interim health advisory (15 µg/L perchlorate in drinking water) to provide guidance to state and local officials in their efforts to address this issue. In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 µg/kg/day and the life stage-specific bodyweight and exposure information (i.e., drinking water intake, RSC) [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2008</Year><RecNum>121</RecNum><DisplayText>(U.S. EPA, 2008a)</DisplayText><record><rec-number>121</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465916938">121</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Interim drinking water health advisory for perchlorate</title></titles><dates><year>2008</year></dates><pub-location>Washington, D.C.</pub-location><isbn>EPA 822-R-08-025</isbn><urls><related-urls><url><style face="underline" font="default" size="100%">https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1004X7Q.TXT</style></url></related-urls></urls></record></Cite></EndNote>]. The HRLs ranged from 1 µg/L to 47 µg/L.

After considering comments on the October 2008 and August 2009 notices, the EPA made a final determination to regulate perchlorate in drinking water in February 2011 [ADDIN EN.CITE <EndNote><Cite><Author>U.S.

EPA</Author><Year>2011</Year><RecNum>69</RecNum><DisplayText>(U.S. EPA, 2011a)</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1438181138">69</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Drinking water: regulatory determination on perchlorate. Federal Register Notice. 76 FR No. 29. Pages 7762-7767. (February 11, 2011) (to be codified at 40 C.F.R pt. 141).</title></titles><volume>2015</volume><number>July 29</number><dates><year>2011</year></dates><pub-location>Washington, D.C.</pub-location><urls><related-urls><url><style face="underline" font="default" size="100%">https://www.federalregister.gov/articles/2011/02/11/2011-2603/drinking-water-regulatory-determination-on-perchlorate</style></url></related-urls></urls></record></Cite></EndNote>]. As a result of the determination, the EPA initiated the process to develop a MCLG and National Primary Drinking Water Regulation (NPDWR) for perchlorate under the SDWA.

In accordance with the SDWA, the Agency requested the EPA Science Advisory Board (SAB) to provide recommendations for how to consider available data in deriving an MCLG for use in developing a NPDWR for perchlorate. The EPA presented the SAB with a description of the general approach used by the Agency to derive an MCLG for non-carcinogenic chemicals. This approach relies on the following equation:

$$MCLG\ \left(\frac{\mu g}{L}\right) = \frac{RfD \times BW}{DWI} \times RSC,$$

where:

RfD = RfD of the contaminant (µg/kg/day) (in the initial assessment for perchlorate, the EPA used NRC's recommended RfD of 0.7 µg/kg/day);

BW = bodyweight (kg); and

DWI = drinking water ingestion rate (L/day).

The EPA also presented information to the SAB about life-stage considerations, physiologically based pharmacokinetic modeling, and epidemiologic and biomonitoring studies. In 2013, the SAB recommended the following:

- Derive a perchlorate MCLG that addresses sensitive life stages through physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling;
- Expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- Utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition – to thyroid hormone changes – and finally to neurodevelopmental impacts; and
- "Extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB, 2013, p. 19).

The SAB's framework incorporates the endpoint of iodide uptake inhibition that was the basis for the RfD as part of this broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes.

In addition, the SAB stated that the EPA should more directly consider thyroid hormone changes as relevant to sensitive life stages; specifically, fetuses of hypothyroxinemic[1] pregnant women and infants and neonates exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><DisplayText>(SAB, 2013)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>]. This is because thyroid hormone insufficiency is known to produce adverse effects on human neurodevelopment, an effect to which the above-mentioned sensitive life stages are especially vulnerable. This direction is different from the conclusions of the NRC report, which based the RfD on the non-adverse effect of reduced iodide uptake and suggested examining pregnant women with hypothyroidism or iodide insufficiency [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>]. The SAB approach focuses on the subtler changes in thyroid hormones (specifically fT4) that are associated with maternal hypothyroxinemia rather than the broader changes in thyroid hormones (both fT4 and TSH) that are associated with hypothyroidism[]. Furthermore, the SAB recommended that the EPA consider available data on potential adverse health effects (i.e., neurodevelopmental outcomes) due to thyroid hormone level perturbations, regardless of the cause of those perturbations [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><DisplayText>(SAB, 2013)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-

[1] The serum-free thyroxine (fT4) value is at the lower end of the population reference range with levels of serum TSH within the population reference range, as opposed to hypothyroidism, which consists of serum fT4 levels below and levels of serum TSH above the respective reference ranges. For the purposes of this report, fT4 and TSH values will be assumed to be measured via the serum unless otherwise stated.

keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>].

To address these recommendations, the EPA revised existing biologically based dose-response (BBDR) and PBPK/PD models [ADDIN EN.CITE <EndNote><Cite><Author>Lumen</Author><Year>2013</Year><RecNum>107</RecNum><DisplayText>(Lumen, Mattie, & Fisher, 2013; U.S. EPA, 2009)</DisplayText><record><rec-number>107</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1450367396">107</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lumen, A.</author><author>Mattie, D.R.</author><author>Fisher, J.W.</author></authors></contributors><titles><title>Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model</title><secondary-title>Toxicological Sciences</secondary-title></titles><periodical><full-title>Toxicological Sciences</full-title></periodical><pages>320-341</pages><volume>133</volume><number>2</number><section>320</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1093/toxsci/kft078</electronic-resource-num></record></Cite><Cite><Author>U.S. EPA</Author><Year>2009</Year><RecNum>205</RecNum><record><rec-number>205</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1467814701">205</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Inhibition of the sodium-iodide symporter by perchlorate: an evaluation of lifestage sensitivity using physiologically based pharmacokinetic (PBPK) modeling (Final Report)</title></titles><dates><year>2009</year></dates><pub-location>Washington, D.C. </pub-location><isbn>EPA/600/R-08/106A</isbn><urls></urls></record></Cite></EndNote>] to create a BBDR model that predicts changes in thyroid hormone (i.e., T4, fT4, and T3) levels as a result of nutritional iodine intake and perchlorate exposure in women prior to pregnancy and early gestation. The EPA originally developed a set of BBDR models that included all sensitive life stages identified by the SAB (i.e., the fetus (by modeling a pregnant mother at 40 gestational weeks (GWs)), neonates, and infants (SAB, 2013)), with the pregnancy model representing the third trimester. These models were peer reviewed in January 2017.[2] Reviewers stressed the importance of developing an early pregnancy model when considering adverse neurodevelopmental impacts.

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[2] For a more detailed discussion of the development of the draft model, its calibration, and dose-response evaluations, please see the draft BBDR model report entitled, *Biologically Based Dose Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analysis.* The report is available through the docket at [HYPERLINK "http://www.regulations.gov"] *(Docket ID No. EPA-HQ-OW-2016-0439).*

The EPA considered the recommendations from the January 2017 peer review and focused on those that were anticipated to be most important for increasing the scientific rigor of the model and modeling results.[3] Model revisions focused on the following key recommendations:

- Extending the model to early pregnancy;
- Incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- Calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- Conducting an uncertainty analysis for key parameters.

Consequently, the MCLG is developed to protect the fetuses of hypothyroxinemic women early in pregnancy. The EPA carried out a subsequent peer review in January 2018 to evaluate updates to the BBDR model and presented several approaches to link the revised perchlorate BBDR model predictions to neurodevelopmental effects. The January 2018 peer review was largely supportive of the efforts described in the Draft Approaches Report, as evidenced by the following from the peer-reviewed final report:

> *The panel commends EPA for the substantial amount of work done in creating the new modeling and preparing the report under review. It was highly responsive to the review comments from a year ago. Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer-reviewed report], the current models are fit-for-purpose to determine an MCLG.*

The purpose of the Draft Approaches Report was to "present the revisions to the BBDR model and alternative approaches that link the revised perchlorate BBDR model predictions to neurodevelopmental effects in response to the prior peer reviews" (U.S. EPA, 2018, p. xi). Additionally, the Draft Approaches Report connected perchlorate doses (from any source) to neurodevelopmental outcomes. The document did not derive an MCLG; rather, it presented alternative approaches that might be used to inform future decisions, including the derivation of an MCLG in accordance with the SDWA.

1.2 Overview of this Report

The remainder of this document describes the approach and inputs the EPA deemed most appropriate to inform an MCLG for perchlorate. The approach to inform the MCLG is a multistep process with many inputs and decision points that will be laid out in this document. In addition, this document provides background information on perchlorate including it chemical and physical properties (Section 2), common uses and environmental fate (Section [REF _Ref529977182 \r \h]), occurrence of perchlorate in drinking water (Section 4), and occurrence of perchlorate in food or other sources (Section [REF

[3] Model revisions are summarized in Section 3 of the Approaches Report, with additional detail provided in Appendix A.

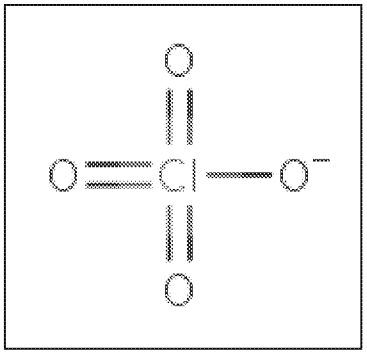
_Ref529977466 \r \h]). To put the MCLG analysis into context, an overview of thyroid hormone physiology is provided along with a description between thyroid hormones and neurodevelopment (Section 6). Section 7 provides a brief overview of perchlorate's mode of action and the evidence evaluating perchlorate's impact on the thyroid. Section [REF _Ref530556732 \r \h] of this report describes the sensitive life stages identified by the SAB and evaluates if protecting the fetuses of hypothyroxinemic pregnant women would also be protective of breast- and formula-fed infants.

Section [REF _Ref530556719 \r \h] is where EPA begins to describe the approach of deriving an MCLG for perchlorate, starting with the selection of an approach to inform the point of departure (POD) for perchlorate (i.e., the selected key parameters for the BBDR model runs and the key epidemiological data selected to inform the MCLG are described). Section [REF _Ref515367288 \r \h * MERGEFORMAT] then describes the EPA's selection of the benchmark response to identify the POD from which an RfD can be derived and Section [REF _Ref515367295 \r \h * MERGEFORMAT] goes on to describe how to translate the identified POD to an RfD by considering and applying appropriate uncertainty factors. Section [REF _Ref515367301 \r \h * MERGEFORMAT] describes the process to convert the RfD to a drinking water concentration by utilizing population-specific exposure factors and the relative source contribution of perchlorate in drinking water, which, ultimately will be deemed the MCLG.

2. Identity: Chemical and Physical Properties

Perchlorate is an inorganic compound containing one chlorine atom bound to four oxygen atoms in a tetrahedral configuration (See [REF _Ref528589635 \h]). As such, perchlorate (ClO_4^-) is an anion that forms salts with most cations. Commonly used perchlorate salts include ammonium perchlorate and potassium perchlorate. Other perchlorate compounds include: sodium perchlorate, aluminum perchlorate, hydrazine perchlorate, hydrogen perchlorate, hydroxylammonium perchlorate, lithium perchlorate, magnesium perchlorate, nitronium perchlorate, and perchloric acid.

Figure [SEQ Figure * ARABIC]. Chemical Structure of Perchlorate



Source: [ADDIN EN.CITE <EndNote><Cite><Author>NLM HSDB</Author><Year>2010</Year><RecNum>2232</RecNum><Prefix>National Library of Medicine's Hazardous Substance Data Bank (</Prefix><Suffix>)</Suffix><DisplayText>(National Library of Medicine's Hazardous Substance Data Bank (NLM HSDB, 2010))</DisplayText><record><rec-number>2232</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543327203">2232</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>NLM HSDB,</author></authors></contributors><titles><title>Ammonium Perchlorate</title></titles><volume>2018</volume><number>November 27</number><dates><year>2010</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~OFnkLk:1</style></url></related-urls></urls></record></Cite></EndNote>]

The chemical structure of perchlorate is shown above ([REF _Ref528589635 \h]). Its physical and chemical properties and Chemical Abstracts Service (CAS) registry numbers for the most common forms of perchlorate are listed in [REF _Ref528589694 \h].

Table [SEQ Table * ARABIC]. Chemical and Physical Properties of Perchlorate

Perchlorate and Its Common Salts					
	Perchlorate	Ammonium perchlorate	Potassium perchlorate	Magnesium perchlorate	Sodium perchlorate
CAS number	14797-73-0	7790-98-9	7778-74-7	10034-81-8	7601-89-0
Molecular Formula	ClO_4^-	NH_4ClO_4	$KClO_4$	$Mg(ClO_4)_2$	$NaClO_4$

Physical and Chemical Properties					
Boiling Point	-	-	400 °C [1]	-	-
Melting Point	-	439 °C [2]	525 °C [4]	250 °C [4]	480 °C [4]
Molecular Weight	99.45 g/mol[a]	117.49 g/mol[b]	138.55 g/mol[a]	223.20 g/mol[d]	122.4 g/mol[a]
Water Solubility	-	200 g/L @ 25°C[c]	15 g/L @ 25°C[c]	99 g/1000g @ 25°C[e]	209 g/100 g @ 25 °C [e]

[a]Budavari [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Year>1996</Year><RecNum>2034</RecNum><DisplayText>(1996)</DisplayText><record><rec-number>2034</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541692268">2034</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Merck & Co. Inc.,</author></authors><secondary-authors><author>Budavari, S.</author></secondary-authors></contributors><titles><secondary-title>The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. </secondary-title></titles><dates><year>1996</year></dates><pub-location>Whitehouse Station, NJ</pub-location><publisher>Merck & Co., Inc.</publisher><urls></urls></record></Cite></EndNote>], [b]NLM HSDB [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>NLM HSDB</Author><Year>2010</Year><RecNum>2232</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>2232</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543327203">2232</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>NLM HSDB,</author></authors></contributors><titles><title>Ammonium Perchlorate</title></titles><volume>2018</volume><number>November 27</number><dates><year>2010</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~OFnkLk:1</style></url></related-urls></urls></record></Cite></EndNote>] [c]Ashford [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ashford</Author><Year>1994</Year><RecNum>2035</RecNum><DisplayText>(1994)</DisplayText><record><rec-number>2035</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541692797">2035</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Ashford, R.D. </author></authors></contributors><titles><secondary-title>Ashford's Dictionary of Industrial Chemicals</secondary-title></titles><dates><year>1994</year></dates><pub-location>London, England</pub-location><publisher>Wavelength Publications Ltd.</publisher><urls></urls></record></Cite></EndNote>], [d]Lide [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Year>2000</Year><RecNum>2036</RecNum><DisplayText>(<style face="italic">CRC Handbook of Chemistry and Physics</style>, 2000)</DisplayText><record><rec-number>2036</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541692958">2036</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><tertiary-authors><author>Lide, D.R. </author></tertiary-authors></contributors><titles><title>CRC Handbook of Chemistry and Physics</title></titles><edition>81</edition><dates><year>2000</year></dates><pub-location>Boca Raton, FL</pub-location><publisher>CRC Press Inc.</publisher><urls></urls></record></Cite></EndNote>], [e]Weast [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Year>1979</Year><RecNum>2037</RecNum><DisplayText>(<style face="italic">Handbook of Chemistry and Physics</style>, 1979)</DisplayText><record><rec-number>2037</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541693035">2037</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><tertiary-authors><author>Weast, R.C.</author></tertiary-authors></contributors><titles><title>Handbook of Chemistry and Physics</title></titles><edition>60</edition><dates><year>1979</year></dates><pub-location>Boca Raton, FL</pub-location><publisher>CRC Press, Inc.</publisher><urls></urls></record></Cite></EndNote>]

3. Uses and Environmental Fate

This section summarizes information pertaining to the uses, manufacture, and environmental fate of perchlorate.

3.1 Production, Use and Occurrence

Ammonium perchlorate is the form of perchlorate most widely used in the United States [ADDIN EN.CITE <EndNote><Cite><Author>Mendiratta</Author><Year>1996</Year><RecNum>2033</RecNum><DisplayText>(Mendiratta, Dotson, & Brooker, 1996)</DisplayText><record><rec-number>2033</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541691180">2033</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Mendiratta, S.K.</author><author>R.L. Dotson</author><author>R.T. Brooker</author></authors><secondary-authors><author>Kroschwitz, J.I. and M. Howe-Grant.</author></secondary-authors></contributors><titles><title>Perchloric acid and perchlorates</title><secondary-title>Kirk-Othmer encyclopedia of chemical technology. </secondary-title></titles><pages>157-170</pages><volume>18</volume><dates><year>1996</year></dates><pub-location>New York, NY</pub-location><publisher>John Wiley & Sons, Inc.</publisher><urls></urls></record></Cite></EndNote>]. It is primarily used as an oxidizer in solid fuels to power rockets, missiles, and fireworks. According to Wang et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Wang</Author><Year>2002</Year><RecNum>2038</RecNum><DisplayText>(2002)</DisplayText><record><rec-number>2038</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541693760">2038</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Wang, H.</author><author>A. Eaton</author><author>B. Narloch</author></authors></contributors><titles><title>National Assessment of Perchlorate Contamination Occurrence</title></titles><pages>Abstract</pages><dates><year>2002</year></dates><pub-location>Denver, CO</pub-location><publisher>Awwa Research Foundation and American Water Works Association</publisher><urls></urls></record></Cite></EndNote>] approximately 90% of perchlorate is manufactured for this application. Data on the amount of ammonium perchlorate used in solid rocket boosters are not available, but the solid propellants used in the booster rockets in the space shuttle were approximately 70% ammonium perchlorate by weight [ADDIN EN.CITE <EndNote><Cite><Author>Conkling</Author><Year>1996</Year><RecNum>2039</RecNum><DisplayText>(Conkling, 1996)</DisplayText><record><rec-number>2039</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541693880">2039</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Conkling, J.A.</author></authors><secondary-authors><author>Kroschwitz, J.I. and M. Howe-Grant.</author></secondary-authors></contributors><titles><title>Pyrotechnics</title><secondary-title>Kirk-Othmer encyclopedia of chemical technology</secondary-title></titles><pages>680-697</pages><volume>20</volume><dates><year>1996</year></dates><pub-location>New York, NY</pub-location><publisher>John Wiley & Sons, Inc.</publisher><urls></urls></record></Cite></EndNote>]. Other perchlorates, such as potassium

perchlorate, are used as oxidizers in solid rocket boosters [ADDIN EN.CITE <EndNote><Cite><Author>Lindner</Author><Year>1993</Year><RecNum>2040</RecNum><DisplayText>(Lindner, 1993)</DisplayText><record><rec-number>2040</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541694015">2040</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Lindner, V.</author></authors><secondary-authors><author>Kroschwitz, J., and M. Howe-Grant.</author></secondary-authors></contributors><titles><title>Explosives and propellants</title><secondary-title>Kirk-Othmer encyclopedia of chemical technology</secondary-title></titles><pages>115-125</pages><volume>10</volume><dates><year>1993</year></dates><pub-location>New York, NY</pub-location><publisher>John Wiley & Sons</publisher><urls></urls></record></Cite></EndNote>].

Perchlorate is also generated during the manufacture and use of pyrotechnic devices such as fireworks [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>]. Potassium perchlorate and ammonium perchlorate are the most commonly used salts in fireworks. Some fireworks components may contain anywhere from 0-70% perchlorate [ADDIN EN.CITE <EndNote><Cite><Author>Sijimol</Author><Year>2014</Year><RecNum>2041</RecNum><DisplayText>(Sijimol & Mohan, 2014)</DisplayText><record><rec-number>2041</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541694150">2041</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sijimol, M.R.</author><author>M. Mohan</author></authors></contributors><titles><title>Environmental impacts of perchlorate with special reference to fireworks - a review. </title><secondary-title>Environ. Monit. Assess.</secondary-title></titles><periodical><full-title>Environ. Monit. Assess.</full-title></periodical><pages>7203-7210</pages><volume>186</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. Ammonium perchlorate is used in small amounts in gun powder [ADDIN EN.CITE <EndNote><Cite><Author>Lindner</Author><Year>1993</Year><RecNum>2040</RecNum><DisplayText>(Lindner, 1993)</DisplayText><record><rec-number>2040</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541694015">2040</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Lindner, V.</author></authors><secondary-authors><author>Kroschwitz, J., and M. Howe-Grant.</author></secondary-authors></contributors><titles><title>Explosives and propellants</title><secondary-title>Kirk-Othmer encyclopedia of chemical technology</secondary-title></titles><pages>115-125</pages><volume>10</volume><dates><year>1993</year></dates><pub-location>New York,

NY</pub-location><publisher>John Wiley & Sons</publisher><urls></urls></record></Cite></EndNote>]. Ammonium and potassium perchlorate are used in signal flares, such as road flares and signaling devices on ships [ADDIN EN.CITE <EndNote><Cite><Author>Conkling</Author><Year>1996</Year><RecNum>2039</RecNum><DisplayText>(Conkling, 1996)</DisplayText><record><rec-number>2039</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541693880">2039</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Conkling, J.A.</author></authors><secondary-authors><author>Kroschwitz, J.I. and M. Howe-Grant.</author></secondary-authors></contributors><titles><title>Pyrotechnics</title><secondary-title>Kirk-Othmer encyclopedia of chemical technology</secondary-title></titles><pages>680-697</pages><volume>20</volume><dates><year>1996</year></dates><pub-location>New York, NY</pub-location><publisher>John Wiley & Sons, Inc.</publisher><urls></urls></record></Cite></EndNote>].

Perchlorate can also be present in lubricating oils, matches, aluminum refining, rubber manufacturing, paint and enamel manufacturing, leather tanning, paper and pulp processing (as an ingredient in bleaching powder), and as a dye mordant [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2006</Year><RecNum>2234</RecNum><DisplayText>(U.S. EPA, 2006)</DisplayText><record><rec-number>2234</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543332964">2234</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Regulatory Determinations Support Document for Selected Contaminants from the Second Drinking Water Contaminant Candidate List (CCL2).</title></titles><number>EPA Report 815-D-06-007</number><dates><year>2006</year></dates><pub-location>Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency, Washington, DC</pub-location><urls></urls></record></Cite></EndNote>]. Potassium perchlorate, mixed with metals such as iron or zirconium, has been used in heat pellets for the activation of reserve battery cells, and lithium and magnesium perchlorate have been used in batteries [ADDIN EN.CITE <EndNote><Cite><Author>Cohen</Author><Year>1993</Year><RecNum>2042</RecNum><DisplayText>(Cohen, 1993)</DisplayText><record><rec-number>2042</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541694926">2042</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Cohen, A.P.</author></authors><secondary-authors><author>Kroschwitz, J.I, and M. Howe-Grant.</author></secondary-authors></contributors><titles><title>Desicants</title><secondary-title>Kirk-Othmer's encyclopedia of chemical technology</secondary-title></titles><pages>1031-1055</pages><volume>7</volume><dates><year>1993</year></dates><pub-location>New York, NY</pub-location><publisher>John Wiley & Sons, Inc.</publisher><urls></urls></record></Cite></EndNote>]. Ammonium perchlorate has been used in temporary adhesives for steel or other metallic plates by mixing with an epoxy resin, which, after curing, forms the adhesive bond between the plates [ADDIN EN.CITE <EndNote><Cite><Author>Vogt</Author><Year>1986</Year><RecNum>2043</RecNum><DisplayText>(Vogt et al., 1986)</DisplayText><record><rec-number>2043</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

timestamp="1541695042">2043</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Vogt, H.</author><author>J. Balej</author><author>J.E. Bennett</author><author>P. Wintzer</author><author>A. Akbar Sheikh</author><author>P. Gallone</author></authors><secondary-authors><author>Gerhartz, W, Y.S. Yamamoto, F.T. Campbell, R. Pfefferkorn, and J.F. Rounsaville</author></secondary-authors></contributors><titles><title>Chlorine oxides and chlorine oxygen acids</title><secondary-title>Ullmann's Encyclopedia of Industrial Chemistry</secondary-title></titles><pages>483-525</pages><volume>A6</volume><dates><year>1986</year></dates><pub-location>New York, NY</pub-location><publisher>VCH Publishers</publisher><urls></urls></record></Cite></EndNote>]. Perchlorate was also used to adjust the ionic strength of electroplating baths in plating razor blades [ADDIN EN.CITE <EndNote><Cite><Author>Schilt</Author><Year>1979</Year><RecNum>2044</RecNum><DisplayText>(Schilt, 1979)</DisplayText><record><rec-number>2044</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541695145">2044</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>Schilt, A.A.</author></authors></contributors><titles><title>Preparation and properties of perchloric acid. Perchloric acid and perchlorates. </title></titles><section>9-63</section><dates><year>1979</year></dates><pub-location>Columbus, OH</pub-location><publisher>The G. Frederick Smith Chemical Company</publisher><urls></urls></record></Cite></EndNote>]. It is not clear to what extent these other uses of perchlorate are still in practice.

During the 1950s and early 1960s, perchlorate was widely used in the treatment of hyperthyroidism, especially for patients with Graves' disease [ADDIN EN.CITE <EndNote><Cite><Author>Von Burg</Author><Year>1995</Year><RecNum>2045</RecNum><DisplayText>(Von Burg, 1995)</DisplayText><record><rec-number>2045</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541695707">2045</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Von Burg, R.</author></authors></contributors><titles><title>Perchlorates</title><secondary-title>J. Appl. Toxicol.</secondary-title></titles><periodical><full-title>J. Appl. Toxicol.</full-title></periodical><pages>237-241</pages><volume>15</volume><dates><year>1995</year></dates><urls></urls></record></Cite></EndNote>]. Perchlorate is currently used in the U.S. to block radioactive technetium in the thyroid and other glands during medical imaging of the brain, blood, and placenta [ADDIN EN.CITE <EndNote><Cite><Author>Gibbs</Author><Year>1998</Year><RecNum>2046</RecNum><DisplayText>(Gibbs et al., 1998)</DisplayText><record><rec-number>2046</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541695841">2046</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Gibbs, J.P.</author><author>R. Ahmad</author><author>K.S. Crump</author><author>D.P. Houck</author><author>T.S. Leveille</author><author>J.E. Findley</author><author>M. Francis</author></authors></contributors><titles><title>Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function</title><secondary-title>J. Occup. Environ. Med. </secondary-title></titles><periodical><full-title>J. Occup. Environ. Med.</full-title></periodical><pages>1072-1082</pages><volume>40</volume><number>12</number><dates><year>1998</year></dates><ur

ls></urls></record></Cite></EndNote>] and as part of a treatment to counter the effects of the drug amiodarone on the thyroid [ADDIN EN.CITE <EndNote><Cite><Author>Martino</Author><Year>2001</Year><RecNum>2047</RecNum><DisplayText>(Martino, Bartalena, Bogazzi, & Braverman, 2001)</DisplayText><record><rec-number>2047</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541695947">2047</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Martino, E.</author><author>L. Bartalena</author><author>F. Bogazzi</author><author>L.E. Braverman</author></authors></contributors><titles><title>The effects of amiodarone on the thyroid</title><secondary-title>Endocr. Rev.</secondary-title></titles><periodical><full-title>Endocr. Rev.</full-title></periodical><pages>240-254</pages><volume>22</volume><number>2</number><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>].

Dasgupta *et al.* [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Dasgupta</Author><Year>2005</Year><RecNum>2048</RecNum><DisplayText>(2005)</DisplayText><record><rec-number>2048</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541729158">2048</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Dasgupta, P.K.</author><author>P.K. Martinelango</author><author>W.A. Jackson</author><author>T.A. Anderson</author><author>K. Tian</author><author>R.W. Tock</author><author>S. Rajagopalan</author></authors></contributors><titles><title>The origin of naturally occurring perchlorate: The role of atmospheric processes</title><secondary-title>Environ. Sci. Technol.</secondary-title></titles><periodical><full-title>Environ. Sci. Technol.</full-title></periodical><pages>1569-1575</pages><volume>39</volume><number>6</number><dates><year>2005</year></dates><urls></urls></record></Cite></EndNote>] detected perchlorate in rain and snow samples, and showed that perchlorate is formed by a variety of simulated atmospheric processes, suggesting that natural, atmospherically-derived perchlorate is present in the environment. This study suggested that perchlorate can be produced in the natural environment by heterogeneous reactions of chlorine compounds with ozone or UV light and by electrical discharge in the air. In a series of experiments, Kang *et al.* [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Kang</Author><Year>2006</Year><RecNum>2049</RecNum><DisplayText>(2006)</DisplayText><record><rec-number>2049</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541729340">2049</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kang, N.</author><author>T.A. Anderson</author><author>W.A. Jackson</author></authors></contributors><titles><title>Photochemical formation of perchlorate from aqueous oxychlorine anions</title><secondary-title>Anal. Chim. Acta </secondary-title></titles><periodical><full-title>Anal. Chim. Acta</full-title></periodical><pages>48-56</pages><volume>567</volume><number>1</number><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>] exposed various chlorine intermediates to UV radiation and produced perchlorate in aqueous salt solutions with initial concentrations of hypochlorite, chlorite, or chlorate between 100 and 10,000 mg/L. Rao *et al.* [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Rao</Author><Year>2007</Year><RecNum>1463</RecNum><Displa

yText>(2007)</DisplayText><record><rec-number>1463</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206442">1463</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rao, B.</author><author>Anderson, T. A.</author><author>Orris, G. J.</author><author>Rainwater, K. A.</author><author>Rajagopalan, S.</author><author>Sandvig, R. M.</author><author>Scanlon, B. R.</author><author>Stonestrom, D. A.</author><author>Walvoord, M. A.</author><author>Jackson, W. A.</author></authors></contributors><titles><title>Widespread natural perchlorate in unsaturated zones of the southwest United States</title><secondary-title>Environmental Science and Technology</secondary-title><alt-title>Environ Sci Technol</alt-title><short-title>Environmental Science and Technology</short-title></titles><periodical><full-title>Environmental Science and Technology</full-title><abbr-1>Environ Sci Technol</abbr-1></periodical><alt-periodical><full-title>Environmental Science and Technology</full-title><abbr-1>Environ Sci Technol</abbr-1></alt-periodical><pages>4522-4528</pages><volume>41</volume><number>13</number><dates><year>2007</year></dates><isbn>ISSN 0013-936X
EISSN 1520-5851</isbn><label>2140862</label><urls></urls><language>English</language></record></Cite></EndNote>] showed that a substantial reservoir of natural perchlorate is present in the vadose (unsaturated) zone of arid and semiarid areas of the U.S., which is capable of producing high levels of perchlorate in groundwater.

Chile possesses caliche ores rich in sodium nitrate ($NaNO_3$), which are also a natural source of perchlorate. These Chilean nitrate salts (saltpeter) have been mined and refined to produce commercial fertilizers, which (before 2001), accounted for about 0.14 percent of U.S. fertilizer application [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2001</Year><RecNum>2235</RecNum><DisplayText>(U.S. EPA, 2001)</DisplayText><record><rec-number>2235</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543335304">2235</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Survey of Fertilizers and Related Materials for Perchlorate (ClO4): Final Report</title></titles><volume>EPA/600/R-01/049</volume><dates><year>2001</year></dates><pub-location>Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH</pub-location><urls></urls></record></Cite></EndNote>]. The U.S. EPA [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>U.S. EPA</Author><Year>2001</Year><RecNum>2235</RecNum><DisplayText>(2001)</DisplayText><record><rec-number>2235</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543335304">2235</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Survey of Fertilizers and Related Materials for Perchlorate (ClO4): Final Report</title></titles><volume>EPA/600/R-01/049</volume><dates><year>2001</year></dates><pub-location>Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH</pub-location><urls></urls></record></Cite></EndNote>] conducted a broad survey of fertilizers and other raw materials and found that all products surveyed were devoid of perchlorate except for those known to contain or to be derived from mined Chilean saltpeter.

Perchlorate production began in the U.S. with the production of magnesium perchlorate in 1928 for use as a desiccant [ADDIN EN.CITE <EndNote><Cite><Author>GFS</Author><Year>1997</Year><RecNum>2055</RecNum><DisplayText>(GFS, 1997)</DisplayText><record><rec-number>2055</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541730164">2055</key></foreign-keys><ref-type name="Catalog">8</ref-type><contributors><authors><author>GFS</author></authors></contributors><titles><title>GFS Chemical Company Catalog</title></titles><dates><year>1997</year></dates><pub-location>Powell, OH</pub-location><publisher>GFS Chemicals, Inc.</publisher><urls></urls></record></Cite></EndNote>]. The total worldwide production of perchlorate was less than 3.6 million pounds until World War II; after World War II, annual perchlorate production increased to 36 million pounds [ADDIN EN.CITE <EndNote><Cite><Author>Mendiratta</Author><Year>1996</Year><RecNum>2033</RecNum><DisplayText>(Mendiratta et al., 1996)</DisplayText><record><rec-number>2033</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541691180">2033</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Mendiratta, S.K.</author><author>R.L. Dotson</author><author>R.T. Brooker</author></authors><secondary-authors><author>Kroschwitz, J.I. and M. Howe-Grant.</author></secondary-authors></contributors><titles><title>Perchloric acid and perchlorates</title><secondary-title>Kirk-Othmer encyclopedia of chemical technology. </secondary-title></titles><pages>157-170</pages><volume>18</volume><dates><year>1996</year></dates><pub-location>New York, NY</pub-location><publisher>John Wiley & Sons, Inc.</publisher><urls></urls></record></Cite></EndNote>] and by 1974, reached 50 million pounds [ADDIN EN.CITE <EndNote><Cite><Author>Vogt</Author><Year>1986</Year><RecNum>2043</RecNum><DisplayText>(Vogt et al., 1986)</DisplayText><record><rec-number>2043</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541695042">2043</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Vogt, H.</author><author>J. Balej</author><author>J.E. Bennett</author><author>P. Wintzer</author><author>A. Akbar Sheikh</author><author>P. Gallone</author></authors><secondary-authors><author>Gerhartz, W, Y.S. Yamamoto, F.T. Campbell, R. Pfefferkorn, and J.F. Rounsaville</author></secondary-authors></contributors><titles><title>Chlorine oxides and chlorine oxygen acids</title><secondary-title>Ullmann's Encyclopedia of Industrial Chemistry</secondary-title></titles><pages>483-525</pages><volume>A6</volume><dates><year>1986</year></dates><pub-location>New York, NY</pub-location><publisher>VCH Publishers</publisher><urls></urls></record></Cite></EndNote>]. In 1994, production data for ammonium perchlorate was estimated at 22 million pounds [ADDIN EN.CITE <EndNote><Cite><Author>Mendiratta</Author><Year>1996</Year><RecNum>2033</RecNum><DisplayText>(Mendiratta et al., 1996)</DisplayText><record><rec-number>2033</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541691180">2033</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Mendiratta, S.K.</author><author>R.L. Dotson</author><author>R.T. Brooker</author></authors><secondary-authors><author>Kroschwitz, J.I. and M. Howe-Grant.</author></secondary-

authors></contributors><titles><title>Perchloric acid and perchlorates</title><secondary-title>Kirk-Othmer encyclopedia of chemical technology. </secondary-title></titles><pages>157-170</pages><volume>18</volume><dates><year>1996</year></dates><pub-location>New York, NY</pub-location><publisher>John Wiley & Sons, Inc.</publisher><urls></urls></record></Cite></EndNote>]. Recent production data for perchlorate are not available. Also, no information on production of perchlorate is available from the Toxic Release Inventory (TRI) database for facilities that produce or process perchlorate because perchlorate is not on the list of chemicals that must be reported.

3.2 Environmental Release

Perchlorate may be released to water from manufacturing and processing facilities. Since wastewater treatment processes (including stripping, precipitation, filtration, oxidation, or aerobic biodegradation) do not effectively remove perchlorate from waste streams, perchlorate in wastewater may eventually be released to surface water [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>]. There is no quantitative information available on the release of ammonium perchlorate from the manufacture, maintenance, or testing of solid rocket propellants, however it has been reported that perchlorate concentrations from these activities may reach the g/L level [ADDIN EN.CITE <EndNote><Cite><Author>Herman</Author><Year>1998</Year><RecNum>2063</RecNum><DisplayText>(Herman & Frankenberger, 1998)</DisplayText><record><rec-number>2063</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541731415">2063</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Herman, D.C.</author><author>W.T. Frankenberger</author></authors></contributors><titles><title>Microbial-mediated reduction of perchlorate in groundwater</title><secondary-title>J. Environ. Qual.</secondary-title></titles><periodical><full-title>J. Environ. Qual.</full-title></periodical><pages>750-754</pages><volume>27</volume><dates><year>1998</year></dates><urls></urls></record></Cite></EndNote>]. According to one report, the amount of ammonium perchlorate released to wastewater from decommissioning rockets during that decade may reach 8.5 million pounds [ADDIN EN.CITE <EndNote><Cite><Author>Buckley</Author><Year>1999</Year><RecNum>2064</RecNum><DisplayText>(Buckley, Sclippa, & Baxter, 1999)</DisplayText><record><rec-number>2064</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541731604">2064</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Buckley, S.G</author><author>G.C. Sclippa</author><author>L.L. Baxter</author></authors></contributors><titles><title>Combustion tests of rocket motor washout material: Focus on air toxics formation potential of asbestos remediation. DE00005953</title></titles><dates><year>1999</year></dates><pub-

location>Albuquerque, NM</pub-location><publisher>Sandia National Laboratories</publisher><urls></urls></record></Cite></EndNote>]. Likewise, there is no quantitative information available on the release of perchlorate from the manufacture or detonation of fireworks. However, elevated levels of perchlorate in water have been measured near fireworks manufacturing facilities in China and India [ADDIN EN.CITE <EndNote><Cite><Author>Sijimol</Author><Year>2014</Year><RecNum>2041</RecNum><DisplayText>(Sijimol & Mohan, 2014)</DisplayText><record><rec-number>2041</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541694150">2041</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sijimol, M.R.</author><author>M. Mohan</author></authors></contributors><titles><title>Environmental impacts of perchlorate with special reference to fireworks - a review. </title><secondary-title>Environ. Monit. Assess.</secondary-title></titles><periodical><full-title>Environ. Monit. Assess.</full-title></periodical><pages>7203-7210</pages><volume>186</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. Isobe et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Isobe</Author><Year>2013</Year><RecNum>2236</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>2236</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543341711">2236</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Isobe, T.</author><author>Ogawa, S.P.</author><author>Sugimoto, R.</author><author>Ramu, K.</author><author>Sudaryanto, A.</author><author>Malarvannan, G.</author><author>Devanathan, G.</author><author>Ramaswamy, B.R.</author><author>Munuswamy, N.</author><author>Ganesh, D.S.</author><author>Sivakumar, J.</author><author>Sethuraman, A.</author><author>Parthasarathy, V.</author><author>Subramanian, A.</author><author>Field, J.</author><author>Tanabe, S.</author></authors></contributors><titles><title>Perchlorate contamination of groundwater from fireworks manufacturing area in South India</title><secondary-title>Environmental Monitoring and Assessment</secondary-title></titles><periodical><full-title>Environmental Monitoring and Assessment</full-title></periodical><pages>5627-37</pages><volume>185</volume><number>7</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>], studied the contamination of perchlorate in groundwater from areas in South India that manufactured fireworks. Concentrations of perchlorate were found to be <0.005-7,690 µg/L in groundwater, <0.005-30.2 µg/L in surface water, and 0.063-0.393 µg/L in tap water. The concentration of perchlorate was higher in the area of the firework factory than in any other location.

Another source of perchlorate in water may be from the release of the compound to the atmosphere and deposition onto the surface of oceans, rivers, lakes, and ponds [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human

Services</publisher><urls></urls></record></Cite></EndNote>]. Perchlorate may also be released to surface water from runoff from sand or soil that contains the compound [ADDIN EN.CITE <EndNote><Cite><Author>Herman</Author><Year>1998</Year><RecNum>2063</RecNum><DisplayText>(Herman & Frankenberger, 1998)</DisplayText><record><rec-number>2063</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541731415">2063</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Herman, D.C.</author><author>W.T. Frankenberger</author></authors></contributors><titles><title>Microbial-mediated reduction of perchlorate in groundwater</title><secondary-title>J. Environ. Qual.</secondary-title></titles><periodical><full-title>J. Environ. Qual.</full-title></periodical><pages>750-754</pages><volume>27</volume><dates><year>1998</year></dates><urls></urls></record></Cite></EndNote>]. This runoff could also result in the presence of perchlorate in underground aquifers [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>].

All forms of perchlorate have very low vapor pressures, therefore perchlorate compounds are not expected to volatilize into air. However, releases of unspent perchlorate to air may occur during its use as a component of solid rocket boosters, as gases are released to provide propulsion of rockets through the atmosphere [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>]. Perchlorates may also be released to the atmosphere during catastrophic failure of rockets [ADDIN EN.CITE <EndNote><Cite><Author>Merrill</Author><Year>1998</Year><RecNum>2069</RecNum><DisplayText>(Merrill & O'Drobinak, 1998)</DisplayText><record><rec-number>2069</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541769248">2069</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Merrill, C.I.</author><author>J.D. O'Drobinak</author></authors></contributors><titles><title>Sea water immersion of GEM II propellant. 1998 JANNAF Propellant Development & Characterization Subcommittee and Safety & Environmental Protection Subcommittee Joint Meeting. Vol. 1. CPIA Publ. </title></titles><pages>561-567</pages><volume>674</volume><dates><year>1998</year></dates><urls></urls></record></C

ite></EndNote>] or during open-burn decommissioning of rocket booster propellants or munitions [ADDIN EN.CITE <EndNote><Cite><Author>Chan</Author><Year>2000</Year><RecNum>2070</RecNum><DisplayText>(Chan, Jr., & Ciaramitaro, 2000)</DisplayText><record><rec-number>2070</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541769380">2070</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Chan, M.L.</author><author>R. Reed Jr.</author><author>D.A. Ciaramitaro</author></authors><secondary-authors><author>Yang, V, T.B. Brill, W-Z. Ren W-Z.</author></secondary-authors></contributors><titles><title>Advances in solid propellant formulations</title><secondary-title>Solid propellant chemistry, combustion, and motor interior ballistics</secondary-title></titles><pages>185-206</pages><volume>185</volume><dates><year>2000</year></dates><pub-location>Reston, VA</pub-location><publisher>American Institute of Aeronautics and Astronautics, Inc.</publisher><urls></urls></record></Cite></EndNote>]. Other sources of perchlorate in air include release of the compound during the detonation of fireworks and other pyrotechnic devices, the wind-borne erosion of contaminated soil, sand, or particulate matter, or the production of perchlorate in the atmosphere after volcanic eruptions [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>].

3.3 Environmental Fate

In water, perchlorate compounds are expected to rapidly dissolve and dissociate into their component ions. The water solubility of perchlorate indicates that it is not expected to adsorb to sediment and organic matter and will not undergo removal through the formation of insoluble metal complexes [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>]. Perchlorate is persistent in the environment [ADDIN EN.CITE <EndNote><Cite><Author>Logan</Author><Year>1998</Year><RecNum>2066</RecNum><DisplayText>(Logan, 1998)</DisplayText><record><rec-number>2066</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541732141">2066</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Logan, B.E.
</author></authors></contributors><titles><title>A review of chlorate- and perchlorate-respiring microorganisms</title><secondary-title>Bioremediat. J. </secondary-title></titles><periodical><full-title>Bioremediat. J.</full-title></periodical><pages>69-79</pages><volume>2</volume><number>2</number><dates><year>1998</year></dates><urls></urls></record></Cite></EndNote>]. *In situ* removal of perchlorate in water has not been demonstrated [ADDIN EN.CITE
<EndNote><Cite><Author>Coates</Author><Year>2000</Year><RecNum>2071</RecNum><DisplayText>(Coates & Anderson, 2000)</DisplayText><record><rec-number>2071</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541769502">2071</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Coates, J.D.</author><author>R.T. Anderson</author></authors></contributors><titles><title>Emerging techniques for anaerobic bioremediation of contaminated environments</title><secondary-title>Trends Biotechnol.</secondary-title></titles><periodical><full-title>Trends Biotechnol.</full-title></periodical><pages>408-412</pages><volume>18</volume><number>10</number><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>], and removal processes such as photooxidation, biodegradation, hydrolysis, or photochemical degradation are not expected to occur [ADDIN EN.CITE
<EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>].

In the laboratory, soil microorganisms have been shown to reduce perchlorate under anaerobic conditions [ADDIN EN.CITE
<EndNote><Cite><Author>Herman</Author><Year>1998</Year><RecNum>2063</RecNum><DisplayText>(Herman & Frankenberger, 1998; Logan, 1998)</DisplayText><record><rec-number>2063</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541731415">2063</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Herman, D.C.</author><author>W.T. Frankenberger</author></authors></contributors><titles><title>Microbial-mediated reduction of perchlorate in groundwater</title><secondary-title>J. Environ. Qual.</secondary-title></titles><periodical><full-title>J. Environ. Qual.</full-title></periodical><pages>750-754</pages><volume>27</volume><dates><year>1998</year></dates><urls></urls></record></Cite><Cite><Author>Logan</Author><Year>1998</Year><RecNum>2066</RecNum><record><rec-number>2066</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541732141">2066</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Logan, B.E.
</author></authors></contributors><titles><title>A review of chlorate- and perchlorate-respiring

microorganisms</title><secondary-title>Bioremediat. J. </secondary-title></titles><periodical><full-title>Bioremediat. J.</full-title></periodical><pages>69-79</pages><volume>2</volume><number>2</number><dates><year>1998</year></dates><urls></urls></record></Cite></EndNote>]. However perchlorate has been shown to be persistent in soil, and thus the significance of this removal process is questionable. One study reported that the necessary criteria for degrading perchlorate in soil are anaerobic conditions, an adequate carbon source, and an active perchlorate-degrading microbial population [ADDIN EN.CITE <EndNote><Cite><Author>Tipton</Author><Year>2003</Year><RecNum>2067</RecNum><DisplayText>(Tipton, Rolston, & Scow, 2003)</DisplayText><record><rec-number>2067</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541732227">2067</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Tipton, D.K.</author><author>D.E. Rolston</author><author>K.M. Scow</author></authors></contributors><titles><title>Bioremediation and biodegradation: Transport and biodegradation of perchlorate in soils</title><secondary-title>J. Environ. Qual. </secondary-title></titles><periodical><full-title>J. Environ. Qual.</full-title></periodical><pages>40-46</pages><volume>32</volume><number>1</number><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>].

Monitoring data suggest that perchlorate may accumulate in living organisms, as the compound was detected in fish, vegetation, insect, amphibian, and rodent samples near a site of known contamination [ADDIN EN.CITE <EndNote><Cite><Author>Smith</Author><Year>2001</Year><RecNum>2072</RecNum><DisplayText>(Smith, Theodorakis, Anderson, & Kendall, 2001)</DisplayText><record><rec-number>2072</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541769635">2072</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Smith, P.N.</author><author>C.W. Theodorakis</author><author>T.A. Anderson</author><author>R.J. Kendall</author></authors></contributors><titles><title>Preliminary assessment of perchlorate in ecological receptors at the Longhorn Army ammunition plant (LHAAP), Karnack, Texas</title><secondary-title>Ecotoxicology</secondary-title></titles><periodical><full-title>Ecotoxicology</full-title></periodical><pages>305-313</pages><volume>10</volume><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>]). However, experimental studies indicate that the bioconcentration of perchlorate in aquatic organisms is low, with bioconcentration factors of 1.854 and 0.70 reported for the Asiatic clam and bluegill, respectively [ADDIN EN.CITE <EndNote><Cite><Author>Dean</Author><Year>2004</Year><RecNum>2073</RecNum><DisplayText>(Dean et al., 2004)</DisplayText><record><rec-number>2073</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541769720">2073</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Dean, K.E.</author><author>R.M. Palachek</author><author>J.M. Noel</author><author>R. Warbritton</author><author>J. Aufderheide</author><author> J. Wireman</author></authors></contributors><titles><title>Development of freshwater water-quality criteria for perchlorate</title><secondary-title>Environ. Toxicol. Chem.</secondary-title></titles><periodical><full-title>Environ. Toxicol. Chem.</full-title></periodical><pages>1441-

1451</pages><volume>23</volume><number>6</number><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>].

3.4 Summary

Perchlorate is primarily used as an oxidizer in solid fuels to power rockets, missiles, and fireworks. Ammonium perchlorate is the form most widely used in the U.S. A source of release of perchlorate to the environment is thought to be from the manufacture of perchlorate for rocket booster engines, and their testing and decommissioning. Perchlorate may also be released to the environment from the manufacture of munitions, the catastrophic failure of booster rockets, and during its use in pyrotechnic devices. It may also be present in the environment from its use as a fertilizer and from natural sources. Perchlorate has been found to be persistent in water and soil and is not removed by most common degradation processes. It is not expected to volatilize to the atmosphere. Perchlorate may accumulate in living organisms; however, bioconcentration factors have been reported to be low.

4. Drinking Water Occurrence

EPA's *Perchlorate Occurrence and Monitoring Document* provides estimates of the baseline perchlorate occurrence in PWSs [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"qUTie4VE","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1675,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":1675,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. After reviewing the available data on perchlorate in drinking water, the EPA determined that the best nationally representative source is data from the Unregulated Contaminant Monitoring Rule 1 (UCMR1). This section summarizes the EPA's perchlorate occurrence analysis [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UCKVzf9d","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1675,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":1675,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The UCMR is a national drinking water monitoring program administered by the EPA. The UCMR1 monitoring cycle included a census of all large CWSs and NTNCWSs (i.e., those serving more than 10,000 people) and a statistical sample of 800 small CWSs and NTNCWSs (i.e., those serving 10,000 people or fewer) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"sOBUvFhD","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1675,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":1675,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The UMCR1 cycle was from 2001-2005; most data collection occurred between 2001 and 2003.

During UMCR1, the EPA obtained perchlorate sample data from systems in all 50 states, the District of Columbia, Tribal Nations, and four U.S. territories (Puerto Rico, Virgin Islands, Guam, and the Northern Mariana Islands). Nearly all systems in either the statistical sample or the census sample responded: 99.6% of small systems and 99.0% of large systems provided data [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"45nk8Bn9","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1675,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":1675,"t

ype":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Systems collected samples at each entry point to the customer distribution system.[4] Entry points are the point of compliance with drinking water standards. Systems can have multiple entry points. Sampling frequency varied by source water: four quarterly samples in a one-year period for surface water systems, and two samples at least 6 months apart for ground water systems [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8NSuLNK0","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1675,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":1675,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The minimum reporting level (MRL) was 4 µg/L [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"k4YEKduX","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1675,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":1675,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

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[4] In response to comments on UCMR1 data quality [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"G1AISvS5","properties":{"formattedCitation":"(U.S. Chamber of Commerce, 2012)","plainCitation":"(U.S. Chamber of Commerce, 2012)","noteIndex":3},"citationItems":[{"id":152,"uris":["http://zotero.org/groups/945096/items/CMDYPKE9"],"uri":["http://zotero.org/groups/945096/items/CMDYPKE9"],"itemData":{"id":152,"type":"article","title":"Information Quality Guidelines (IQG) Request for Correction","publisher":"Letter to USEPA. September.","author":[{"family":"U.S. Chamber of Commerce","given":""}],"issued":{"date-parts":[["2012"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. the EPA reviewed the UCMR1 data to identify instances where source water monitoring samples were accompanied by corresponding 'downstream' entry point monitoring samples. In these instances, only the entry point samples provide the perchlorate concentration in water delivered to customers. Therefore, the 2013 version of the UCMR1 dataset excludes these types of source water samples [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"DTSSVkcz","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":3},"citationItems":[{"id":1675,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":1675,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The maximum reported concentration of perchlorate was 420 µg/L, which was found in a single surface water sample from a PWS in Puerto Rico. The average concentration of perchlorate for those samples with positive detections for perchlorate was 9.9 µg/L and the median concentration was 6.4 µg/L.

The summary statistics in [REF _Ref528590138 \h] show total samples, entry points, and systems in the UCMR1 perchlorate dataset. It also shows the number of reported perchlorate detections (≥ 4 µg/L) and the number of detections strictly greater than the MRL of 4 µg/L.

Table [SEQ Table * ARABIC]. UCMR1 Data Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total samples	3,295	30,837	34,132
• Detections ≥ 4 µg/L	15	525	540
• Detections > 4 µg/L	15	510	525
Total entry points	1,454	13,482	14,936
• Detections ≥ 4 µg/L	8	328	336
• Detections > 4 µg/L	8	314	322
Total systems	797	3,068	3,865
• Detections ≥ 4 µg/L	8	141	149
• Detections > 4 µg/L	8	136	144

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UAoGFPZv","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1675,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":1675,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

[REF _Ref528590178 \h] shows the populations that correspond with the occurrence summary in [REF _Ref528590138]. The entry point population estimates reflect the assumption that system population is uniformly distributed across entry points; e.g., the entry point population for a system with two entry points is one-half the total system population.

Table [SEQ Table * ARABIC]. UCMR1 Data Service Population Summary Statistics

Item	Small System Sample	Large System Census	Sum
Total entry point population	2,760,570	222,853,101	225,613,671
• Detections ≥ 4 µg/L	9,484	4,063,241	4,072,725
• Detections > 4 µg/L	9,484	3,965,473	3,974,957
Total system population	2,760,570	222,853,101	225,613,671
• Detections ≥4 µg/L	13,483	16,159,082	16,172,565
• Detections > 4 µg/L	13,483	15,922,821	15,936,304

Source: [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ChxDKgDr","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1675,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":1675,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

Because the UCMR1 data are well over a decade old, the EPA considered potential sources of uncertainty because of changes between current conditions and conditions at the time of data collection. One important change is the adoption of regulatory limits in two states: Massachusetts adopted a drinking water standard for perchlorate of 2 µg/L in 2006 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8DPpSrv3","properties":{"formattedCitation":"(MassDEP, 2006)","plainCitation":"(MassDEP, 2006)","noteIndex":0},"citationItems":[{"id":151,"uris":["http://zotero.org/groups/945096/items/9893MBZH"],"uri":["http://zotero.org/groups/945096/items/9893MBZH"],"itemData":{"id":151,"type":"personal_communication","title":"Letter to Public Water Suppliers concerning new perchlorate regulations","URL":"https://www.mass.gov/lists/perchlorate-background-information-and-standards#perchlorate---final-standards-","author":[{"family":"MassDEP","given":""}],"issued":{"date-parts":[["2006"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and California promulgated a drinking water standard of 6 µg/L in 2007 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cfr6HNhg","properties":{"formattedCitation":"(California Department of Public Health, 2007)","plainCitation":"(California Department of Public Health, 2007)","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/groups/945096/items/RA45NKLQ"],"uri":["http://zotero.org/groups/945096/items/RA45NKLQ"],"itemData":{"id":150,"type":"personal_communication","title":"State Adoption of a Perchlorate Standard","URL":"https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/perchlorate/AdoptionMemotoWaterSystems-10-2007.pdf","author":[{"family":"California

Department of Public Health","given":""}],"issued":{"date-parts":[["2007"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Systems in these states cannot exceed these limits. Subsequently EPA re-evaluated and excluded the California and Massachusetts from the remainder of this analysis. [REF _Ref528590235 \h * MERGEFORMAT] summarizes the UCMR1 data pursuant to this assumption.

Table [SEQ Table * ARABIC]. UCMR1 Data Summary Statistics, Excluding California and Massachusetts

Item	Small System Sample	Large System Census	Sum
Total samples	2,984	21,128	24,112
• Detections ≥ 4 µg/L	13	206	219
• Detections > 4 µg/L	13	195	208
Total entry points	1,327	9,118	10,445
• Detections ≥ 4 µg/L	7	159	166
• Detections > 4 µg/L	7	149	156
Total systems	737	2591	3,328
• Detections ≥ 4 µg/L	7	91	98
• Detections > 4 µg/L	7	91	98
Total entry point population	2,537,888	183,525,431	186,063,319
• Detections ≥ 4 µg/L	5,430	1,760,855	1,766,285
• Detections > 4 µg/L	9,484	3,965,473	3,974,957
Total system population	2,537,888	183,525,431	186,063,319
• Detections ≥4 µg/L	9,429	7,762,593	7,772,022
• Detections > 4 µg/L	13,483	15,922,821	15,936,304

Another change involves remediation efforts to reduce the sources of perchlorate in drinking water. USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NaOQHInh","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1675,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":1675,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] describes remediation efforts that have effectively reduced perchlorate levels in the Colorado River water from a range of 4 µg/L to 9 µg/L during the UCMR1 data collection period to 1 µg/L to 2 µg/L after 2009.

Both of these changes tend to reduce current perchlorate concentrations compared to the levels observed in the UCMR1 data. A third type of change that has an uncertain impact on occurrence is the change in the universe of systems over time. Some systems operating during the UCMR1 data

collection period are now inactive. There are also new systems that were not operating during the UCMR1 period.

5. Exposure or Occurrence from Food and Other Sources

This section summarizes studies of perchlorate occurrence in food, as well as the most recent perchlorate exposure estimates from the consumption of food (Section [REF _Ref531260962 \r \h]). This section also summarizes studies of the occurrence of perchlorate in air and soil (Section [REF _Ref531261023 \r \h] and [REF _Ref531261025 \r \h]), as well as studies focused on other environmental and occupational sources of perchlorate exposure (Sections [REF _Ref531261047 \r \h] and [REF _Ref531261049 \r \h]).

5.1 Exposure/Occurrence from Food

Although perchlorate has been detected in many different kinds of food, studies of perchlorate in food generally show the highest levels of perchlorate in produce and milk products. A study by the European Food Safety Authority found relatively high mean occurrence values in dried products such as "Tea and herbs for infusion" (324 µg /kg) and "Herbs, spices and condiments" (63 µg /kg), as well as in fresh vegetables such as "Radishes" (117 µg/kg), "Rocket salad, rucola" (75 µg /kg) and "Spinach (fresh)" (132 µg/kg) [ADDIN EN.CITE <EndNote><Cite><Author>Arcella</Author><Year>2017</Year><RecNum>2217</RecNum><DisplayText>(Arcella, Binaglia, & Vernazza, 2017)</DisplayText><record><rec-number>2217</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1542749308">2217</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Arcella, Davide</author><author>Binaglia, Marco</author><author>Vernazza, Francesco</author></authors></contributors><titles><title>Dietary exposure assessment to perchlorate in the European population</title><secondary-title>EFSA Journal</secondary-title></titles><periodical><full-title>EFSA Journal</full-title></periodical><volume>15</volume><number>10</number><dates><year>2017</year></dates><isbn>18314732
18314732</isbn><urls></urls><electronic-resource-num>10.2903/j.efsa.2017.5043</electronic-resource-num></record></Cite></EndNote>]. [HYPERLINK \l "_ENREF_71" \o "Lau, 2013 #2224"] found that consumption mass of "Milk products" predicted higher urinary perchlorate concentrations in children age 6 to 11 years using National Health and Nutrition Examination Survey (NHANES)[5] data. Lau et al. (2013) [HYPERLINK \l "_ENREF_71" \o "Lau, 2013 #2224"] also found a statistically significant relationship between consumption mass of "Milk products" and higher urinary perchlorate concentrations in adults, along with consumption mass of "Vegetables" and "Dark-green leafy vegetables". Additionally, the FDA Exploratory Survey on Perchlorate in Food [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Food and Drug Administration (FDA)</Author><Year>2015</Year><RecNum>1916</RecNum><DisplayText>(2015)</DisplayText><record><rec-number>1916</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519436">1916</key></foreign-

[5] The NHANES is run by the Centers for Disease Control and Prevention's National Center for Health Statistics and was designed to collect information on the health and nutritional status of the U.S. civilian, non-institutionalized population through in-home interviews and physical examinations

keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>Food and Drug Administration (FDA),</author></authors></contributors><titles><title>Preliminary estimation of perchlorate dietary exposure based on FDA 2004/2005 exploratory data</title></titles><dates><year>2015</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">https://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077653.htm</style></url></related-urls></urls></record></Cite></EndNote>] found that milk contributed the highest perchlorate exposure (47% of total exposure) for the mean population aged 2 years and older. [HYPERLINK \l "_ENREF_74" \o "Lee, 2012 #2225"] found that the highest average concentration of perchlorate for Korean food was found in dairy products (6.34 µg/kg), with over 85% of samples having a detection. [HYPERLINK \l "_ENREF_74" \o "Lee, 2012 #2225"] also found that spinach was the food with the highest average perchlorate concentration (39.9 µg/kg) followed by tomatoes (19.8 µg/kg) and green pumpkin (11.6 µg/kg). Alomirah et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Alomiraha</Author><Year>2016</Year><RecNum>2239</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>2239</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543344227">2239</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alomiraha, H.F.</author><author>Al-Zenkia, S.F.</author><author>Alaswada, M.C.</author><author>Alruwaiha, N.A.</author><author>Wub, Q.</author><author>Kannanb, K.</author></authors></contributors><titles><title>Widespread occurrence of perchlorate in water, foodstuffs and human urine collected from Kuwait and its contribution to human exposure</title><secondary-title>Food Additives and Contaminants</secondary-title></titles><periodical><full-title>Food Additives and Contaminants</full-title><abbr-1>Food Addit Contam</abbr-1></periodical><pages>1016-1025</pages><volume>33</volume><number>6</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] found that leafy vegetables accounted for 36.2% of perchlorate exposure among the Kuwait population, with fruits contributing 15.3% and non-leafy vegetables contributing 10.1%. In addition to the perchlorate detected in produce and milk products, perchlorate has also been detected in beer, wine, dietary supplements, and vitamins [ADDIN EN.CITE <EndNote><Cite><Author>Aribi</Author><Year>2006</Year><RecNum>2081</RecNum><DisplayText>(Aribi, Blanc, Antonsen, & Sakuma, 2006; Snyder, Pleus, Vanderford, & Holady., 2006)</DisplayText><record><rec-number>2081</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541770654">2081</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Aribi, H.</author><author>Y.J.C. Le Blanc</author><author>S. Antonsen</author><author>T. Sakuma</author></authors></contributors><titles><title>Analysis of Perchlorate in Foods and Beverages by Ion Chromatography Couple with Tandem Mass Spectrometry (IC-ESI-MS/MS)</title><secondary-title>Anal. Chim. Acta</secondary-title></titles><periodical><full-title>Anal. Chim. Acta</full-title></periodical><pages>39-47</pages><volume>567</volume><number>1</number><dates><year>2006</year></dates><urls></urls></record></Cite><Cite><Author>Snyder</Author><Year>2006</Year><RecNum>2082</RecNum><record><rec-number>2082</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541770749">2082</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Snyder,

S.A.</author><author>R.C. Pleus</author><author>B.J. Vanderford</author><author>J.C. Holady.</author></authors></contributors><titles><title>Perchlorate and chlorate in dietary supplements and flavor enhancing ingredients</title><secondary-title>Anal. Chim. Acta. </secondary-title></titles><periodical><full-title>Anal. Chim. Acta.</full-title></periodical><pages>26-32</pages><volume>567</volume><number>1</number><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>].

The most recent and most comprehensive information available on total daily exposure to perchlorate through the diet for the U.S. population comes from an analysis carried out by scientists at the FDA in the Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] study, which combines perchlorate food contamination data from the FDA's Total Diet Study (TDS) with food consumption data from CDC's What We Eat in America (WWEIA). The Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] analysis was modeled after a previous FDA study using TDS perchlorate data to estimate mean intake of perchlorate for 14 age/sex groups [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The EPA also performed a follow-on study to the Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and

iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] analysis to estimate perchlorate intake using the same methods but for additional populations of interest. This remainder of this section describes these EPA and FDA perchlorate in food analyses.

5.1.1 FDA Total Diet Study

The Food and Drug Administration's (FDA's) Total Diet Study (TDS) is an ongoing FDA program that collects information on levels of various contaminants, including perchlorate, which occur in food and beverages commonly consumed by the U.S. population [ADDIN EN.CITE <EndNote><Cite><Author>U.S. FDA</Author><Year>2015</Year><RecNum>2006</RecNum><DisplayText>(U.S. FDA, 2015)</DisplayText><record><rec-number>2006</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530038884">2006</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>U.S. FDA,</author></authors></contributors><titles><title>Total diet study — study design</title></titles><dates><year>2015</year></dates><urls><related-urls><url>http://www.fda.gov/food/foodscienceresearch/totaldietstudy/ucm184232.htm#</url></related-urls></urls></record></Cite></EndNote>]. To estimate the levels of contaminants in these food products, the FDA buys these foods as a consumer would, prepares them as directed,[6] and then analyzes the prepared foods for levels of the contaminants of interest. This process yields nationally representative estimates of contaminant levels in more than 280 kinds of food and beverages. For the purposes of estimating perchlorate concentrations in food, TDS data on perchlorate were collected from 2008 to 2012. These years of TDS perchlorate data were used for both the Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]study, as well as the EPA perchlorate in food analysis. FDA also included perchlorate as an analyte in TDS baby foods in 2005 and in all other TDS foods in 2006, which were used as the basis for the earlier Murray et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] study that served as the

[6] The FDA prepares their samples using deionized water.

model for carrying out the Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] analysis.

5.1.2 Abt et al. (2016)

The aim of the Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] study was to use the available TDS data to estimate daily perchlorate and iodine intake rates for 14 age/sex groups. The study was intended to provide an update to the Murray et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] study, which also estimated perchlorate exposure for the same 14 sex/age groups using 2005 to 2006 TDS data combined with food consumption data from USDA's 1994 to 1996 and 1998 Continuing Survey of Food Intakes by Individuals.

The Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-

title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] study instead combined 2008 to 2012 TDS food contaminant data with food consumption and demographic data from the 2007 to 2012 NHANES [ADDIN EN.CITE <EndNote><Cite><Author>CDC</Author><Year>2007-2008, 2009-2010, 2011-2012</Year><RecNum>2005</RecNum><DisplayText>(CDC & NCHS, 2007-2008, 2009-2010, 2011-2012)</DisplayText><record><rec-number>2005</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530038652">2005</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>CDC,</author><author>NCHS</author></authors></contributors><titles><title>National health and nutrition examination survey data</title></titles><dates><year>2007-2008, 2009-2010, 2011-2012</year></dates><urls><related-urls><url>http://www.cdc.gov/nchs/nhanes.htm</url></related-urls></urls></record></Cite></EndNote>]. The dietary intake measurement component of the survey is called What We Eat in America (WWEIA) and provides 24-hour food diary data. Dietary data are collected for up to two days for each respondent [ADDIN EN.CITE <EndNote><Cite><Author>CDC</Author><Year>2007-2008, 2009-2010, 2011-2012</Year><RecNum>2005</RecNum><DisplayText>(CDC & NCHS, 2007-2008, 2009-2010, 2011-2012)</DisplayText><record><rec-number>2005</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530038652">2005</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>CDC,</author><author>NCHS</author></authors></contributors><titles><title>National health and nutrition examination survey data</title></titles><dates><year>2007-2008, 2009-2010, 2011-2012</year></dates><urls><related-urls><url>http://www.cdc.gov/nchs/nhanes.htm</url></related-urls></urls></record></Cite></EndNote>].

With four samples taken for each food for each year of data in the TDS, the study had a total of 20 perchlorate samples for each of the 282 foods in the TDS. Many of the measurements of perchlorate in the TDS fall below the limit of detection (LOD). In order to account for values below the LOD, Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] used a method suggested by WHO to calculate both the lower and upper bound concentrations in the foods by substituting all values below the LOD with zero to estimate the lower bound, and substituting all values below the LOD with the LOD to estimate the upper bound [ADDIN EN.CITE <EndNote><Cite><Author>European Food Safety Authority</Author><Year>2010</Year><RecNum>2007</RecNum><DisplayText>(Authority,

2010)</DisplayText><record><rec-number>2007</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530039022">2007</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>European Food Safety Authority</author></authors></contributors><titles><title>Management of left-censored data in dietary exposure assessment of chemical substances</title><secondary-title>EFSA Journal</secondary-title></titles><periodical><full-title>EFSA Journal</full-title></periodical><pages>1-96</pages><number>8</number><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] also implemented a Bayesian method for substituting values below the LOD known as the clustered zero-inflated lognormal (CZILN) method, which groups foods with similar exposure profiles together and models the values below the LOD based on the trends of the known values of the grouped foods above the LOD. Once these methods were applied to each of the values below the LOD, average perchlorate concentrations for each TDS food were calculated and carried forward for use in the perchlorate intake analysis.

The WWEIA food diary data include each individual food that was consumed during each 24-hour study period, as well as the amount of each food consumed measured in grams. For a large subset of respondents, food diary data are available for two days. For this analysis, the study authors included only participants with two days of dietary survey data, and used the appropriate NHANES survey weights for this segment of the dataset. Foods that are included in the TDS are not characterized and coded exactly the same way as the foods in the WWEIA food diaries. Therefore, it is necessary to use expert judgement to match the TDS foods with the WWEIA foods. The study authors developed a "matching" file that enabled them to link each food consumed in the 2007 to 2012 WWEIA data with one of the 282 foods in the 2008 to 2012 TDS data. Once each consumed food in the WWEIA was linked to a perchlorate concentration from TDS, the authors were able to develop estimates of per-capita mean daily intake for each participant based on both the WHO method for values below the LOD, as well as the CZILN method, by adding up the total perchlorate intake for each of the two days of food intake in the WWEIA, and calculating the average total perchlorate intake between the two days. CZILN estimated and WHO method lower and upper bound estimated mean daily intake results for the 14 age/sex groups from Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] are reported in [REF _Ref528663468 \h].

Table [SEQ Table * ARABIC]. CZILN and WHO Method Lower- and Upper-bound Perchlorate Intakes from Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]

Population Group		Total Average Intake (µg/person/day)			Total Average Intake (µg/kg/day)		
		Lower-bound	Upper-bound	CZILN Method	Lower-bound	Upper-bound	CZILN Method
Infants	6-11 mo	3.3	3.6	3.2	0.36	0.39	0.36
Children	2 yr	6.1	6.6	6.0	0.44	0.48	0.43
Children	6 yr	6.5	7.3	6.4	0.28	0.31	0.28
Children	10 yr	6.1	7.1	6.2	0.16	0.18	0.16
Teenage Girls	14-16 yr	5.7	6.8	6.0	0.10	0.12	0.10
Teenage Boys	14-16 yr	7.4	8.7	7.4	0.11	0.13	0.11
Women	25-30 yr	6.3	7.8	6.5	0.09	0.11	0.09
Men	25-30 yr	7.8	10.0	8.3	0.09	0.12	0.10
Women	40-45 yr	6.6	8.3	6.9	0.09	0.12	0.10
Men	40-45 yr	9.0	11.2	9.3	0.10	0.13	0.10
Women	60-65 yr	7.5	9.1	7.4	0.10	0.12	0.10
Men	60-65 yr	7.9	9.9	8.3	0.09	0.11	0.09
Women	70+ yr	6.5	7.7	6.6	0.10	0.11	0.10
Men	70+ yr	7.6	9.0	7.7	0.09	0.11	0.09

Source: Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]

The Abt et al [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] study found that 97% of the TDS foods had detectable levels of perchlorate in at least one sample , which is higher than was previously reported in the Murray et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] study that used 2005 to 2006 TDS data. The authors concluded that the majority of perchlorate intake for infants comes from baby food (56%), while the other child and teenage groups had the largest proportion of perchlorate intake from consumption of dairy (from 53% of perchlorate intake in two year old children, to 28% of perchlorate intake in girls age 14 to 16 years). Adult groups had the largest proportion of their perchlorate intake from either "meat, poultry, fish" or "vegetables".

5.2 Occurrence in Air

Perchlorate in wet deposition was measured at 26 sites across the U.S. in a 3-year period (2004-2007) [ADDIN EN.CITE <EndNote><Cite><Author>Rajagopalan</Author><Year>2009</Year><RecNum>2084</RecNum><DisplayText>(Rajagopalan et al., 2009)</DisplayText><record><rec-number>2084</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541770962">2084</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rajagopalan, S.</author><author>T. Anderson</author><author>S. Cox</author><author>G. Harvey</author><author>Q. Cheng</author><author>W.A. Jackson</author></authors></contributors><titles><title>Perchlorate in wet deposition across North America</title><secondary-title>Environ. Sci. Technol. </secondary-title></titles><periodical><full-title>Environ. Sci. Technol.</full-title></periodical><pages>616-622</pages><volume>43</volume><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. Perchlorate concentrations varied from < 5 ng/L to a high of 102 ng/L, with a mean

of 14.1 ± 13.5 ng/L (standard deviation). Perchlorate concentrations in wet deposition were highest in May-August and lowest in December-February and generally increased with distance from the coast. Perchlorate concentrations were also significantly associated with other monitored ions (calcium, sodium, potassium, ammonia, nitrate, chlorine, and sulfate).

Several studies [ADDIN EN.CITE ADDIN EN.CITE.DATA] have documented the increased concentration in air due to July 4th fireworks, including deposition on soil. Wu et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Wu</Author><Year>2011</Year><RecNum>2087</RecNum><DisplayText>(2011)</DisplayText><record><rec-number>2087</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541771183">2087</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Wu, Q.</author><author>J.F. Oldi</author><author>K. Kanna</author></authors></contributors><titles><title> Fate of Perchlorate in Man-made Reflecting Pond Following a Fireworks Display in Albany, New York, USA</title><secondary-title>Environmental Toxicology and Chemistry</secondary-title></titles><periodical><full-title>Environmental Toxicology and Chemistry</full-title><abbr-1>Environ Toxicol Chem</abbr-1></periodical><pages>2449-2455</pages><volume>30</volume><number>11</number><dates><year>2011</year></dates><urls></urls></record></Cite></EndNote>] noted that aerial deposition from fireworks displays ranged from 670 to 2.620 g/ha.

5.3 Occurrence in Soil

The maximum reported perchlorate concentration in soil at 27 DoD facilities in 12 states ranged from approximately 32 to 2,000,000 ppb. Maximum reported perchlorate concentrations in sediment ranged from 17 to 230 ppb at four Federal defense facilities [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2005</Year><RecNum>2237</RecNum><DisplayText>(U.S. EPA, 2005b)</DisplayText><record><rec-number>2237</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543342576">2237</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Known perchlorate releases in the U.S. - March 25, 2005</title></titles><dates><year>2005</year></dates><pub-location>Washington, D.C.</pub-location><publisher>U.S. Environmental Protection Agency</publisher><urls></urls></record></Cite></EndNote>] and perchlorate levels in four of 12 sediment samples at an ammunition plant ranged from 12 to 704 µg/L [ADDIN EN.CITE <EndNote><Cite><Author>Smith</Author><Year>2001</Year><RecNum>2072</RecNum><DisplayText>(Smith et al., 2001)</DisplayText><record><rec-number>2072</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541769635">2072</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Smith, P.N.</author><author>C.W. Theodorakis</author><author>T.A. Anderson</author><author>R.J. Kendall</author></authors></contributors><titles><title>Preliminary assessment of perchlorate in ecological receptors at the Longhorn Army ammunition plant (LHAAP), Karnack, Texas</title><secondary-title>Ecotoxicology</secondary-title></titles><periodical><full-title>Ecotoxicology</full-title></periodical><pages>305-

313</pages><volume>10</volume><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>]. Perchlorate was detected in 38% of 113 soil samples and 93% of sediment samples collected from the Lake Mead area of Nevada with average/maximum concentrations of 57.7/1,470 mg/kg and 12.8/56.0 mg/kg, respectively [ADDIN EN.CITE <EndNote><Cite><Author>Dean</Author><Year>2004</Year><RecNum>2073</RecNum><DisplayText>(Dean et al., 2004)</DisplayText><record><rec-number>2073</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541769720">2073</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Dean, K.E.</author><author>R.M. Palachek</author><author>J.M. Noel</author><author>R. Warbritton</author><author>J. Aufderheide</author><author> J. Wireman</author></authors></contributors><titles><title>Development of freshwater water-quality criteria for perchlorate</title><secondary-title>Environ. Toxicol. Chem.</secondary-title></titles><periodical><full-title>Environ. Toxicol. Chem.</full-title></periodical><pages>1441-1451</pages><volume>23</volume><number>6</number><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]. A mean perchlorate concentration of 24.7 µg/g in 51 soil samples was reported from three sites in Nevada [ADDIN EN.CITE <EndNote><Cite><Author>Smith</Author><Year>2004</Year><RecNum>2088</RecNum><DisplayText>(Smith, Lu, McMurry, & Anderson, 2004)</DisplayText><record><rec-number>2088</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541771346">2088</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Smith, P.N.</author><author>Y. Lu</author><author>S.T. McMurry</author><author>T.A. Anderson</author></authors></contributors><titles><title>Perchlorate in water, soil, vegetation, and rodents collected from the Las Vegas Wash, Nevada, U.S.A.</title><secondary-title>Environ. Pollut.</secondary-title></titles><periodical><full-title>Environ. Pollut.</full-title></periodical><pages>121-127</pages><volume>132</volume><number>1</number><dates><year>2004</year></dates><urls></urls></record></Cite></EndNote>]while soil samples from a tobacco field that had been fertilized with products derived from Chilean caliches reported perchlorate at a concentration of 340 µg/g [ADDIN EN.CITE <EndNote><Cite><Author>Ellington</Author><Year>2001</Year><RecNum>2056</RecNum><DisplayText>(Ellington et al., 2001)</DisplayText><record><rec-number>2056</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541730269">2056</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ellington, J.J.</author><author>N.L. Wolfe</author><author>A.W. Garrison</author><author>J.J. Evans</author><author>J.K Avants</author><author>Q. Teng</author></authors></contributors><titles><title>Determination of perchlorate in tobacco plants and tobacco products</title><secondary-title>Environ. Sci. Technol.</secondary-title></titles><periodical><full-title>Environ. Sci. Technol.</full-title></periodical><pages>3213-3218</pages><volume>35</volume><number>15</number><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>].Natural perchlorate, unrelated to the Chilean source, has been widely detected in the arid U.S. Southwest. Concentrations in unconsolidated surficial material from Death Valley, CA range from 0.25-1.7 mg/kg (Jackson et al. 2010).

5.4 Other Residential Exposures

Perchlorate has been detected in tobacco products [ADDIN EN.CITE <EndNote><Cite><Author>Ellington</Author><Year>2001</Year><RecNum>2056</RecNum><DisplayText>(Ellington et al., 2001)</DisplayText><record><rec-number>2056</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541730269">2056</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ellington, J.J.</author><author>N.L. Wolfe</author><author>A.W. Garrison</author><author>J.J. Evans</author><author>J.K Avants</author><author>Q. Teng</author></authors></contributors><titles><title>Determination of perchlorate in tobacco plants and tobacco products</title><secondary-title>Environ. Sci. Technol.</secondary-title></titles><periodical><full-title>Environ. Sci. Technol.</full-title></periodical><pages>3213-3218</pages><volume>35</volume><number>15</number><dates><year>2001</year></dates><urls></urls></record></Cite></EndNote>], resulting in exposure to individuals who smoke, and is a component of gunpowder, exposing individuals who reload their own ammunition [ADDIN EN.CITE <EndNote><Cite><Author>Lindner</Author><Year>1993</Year><RecNum>2040</RecNum><DisplayText>(Lindner, 1993)</DisplayText><record><rec-number>2040</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541694015">2040</key></foreign-keys><ref-type name="Encyclopedia">53</ref-type><contributors><authors><author>Lindner, V.</author></authors><secondary-authors><author>Kroschwitz, J., and M. Howe-Grant.</author></secondary-authors></contributors><titles><title>Explosives and propellants</title><secondary-title>Kirk-Othmer encyclopedia of chemical technology</secondary-title></titles><pages>115-125</pages><volume>10</volume><dates><year>1993</year></dates><pub-location>New York, NY</pub-location><publisher>John Wiley & Sons</publisher><urls></urls></record></Cite></EndNote>]. Small amounts of perchlorate are used in different types of medical imaging, resulting in exposure to members of the population undergoing health tests [ADDIN EN.CITE <EndNote><Cite><Author>Gibbs</Author><Year>1998</Year><RecNum>2046</RecNum><DisplayText>(Gibbs et al., 1998)</DisplayText><record><rec-number>2046</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541695841">2046</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Gibbs, J.P.</author><author>R. Ahmad</author><author>K.S. Crump</author><author>D.P. Houck</author><author>T.S. Leveille</author><author>J.E. Findley</author><author>M. Francis</author></authors></contributors><titles><title>Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function</title><secondary-title>J. Occup. Environ. Med. </secondary-title></titles><periodical><full-title>J. Occup. Environ. Med.</full-title></periodical><pages>1072-1082</pages><volume>40</volume><number>12</number><dates><year>1998</year></dates><urls></urls></record></Cite></EndNote>]. Wan et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Wan</Author><Year>2015</Year><RecNum>2238</RecNum><DisplayText>(2015)</DisplayText><record><rec-number>2238</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543342876">2238</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Wan, Y.</author><author>Wu, Q.</author><author>Abualnaja, K.O.</author><author>Asimakopoulos, A.G.</author><author>Covaci, A.</author><author>Gevao, B.</author><author>Johnson-Restrepo, B.</author><author>Kumosani, T.A. </author><author>Malarvannan, G.</author><author>Moon, H. </author><author>Nakata, H.</author><author>Sinha, R.K. </author><author>Minh, T.B. </author><author>Kannan, K.</author></authors></contributors><titles><title>Occurrence of perchlorate in indoor dust from the United States and eleven other countries: Implications for human exposure</title><secondary-title>Environmental International </secondary-title></titles><periodical><full-title>Environmental International</full-title></periodical><pages>166-171</pages><volume>75</volume><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>] collected dust samples from various microenvironments. Concentrations of indoor dust ranged from 0.03-1.18 µg/g. They estimated a median daily intake of perchlorate for toddlers through ingestion of dust to be 1.89 ng/kg bodyweight/day in the United States [ADDIN EN.CITE <EndNote><Cite><Author>Wan</Author><Year>2015</Year><RecNum>2238</RecNum><DisplayText>(Wan et al., 2015)</DisplayText><record><rec-number>2238</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543342876">2238</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Wan, Y.</author><author>Wu, Q.</author><author>Abualnaja, K.O.</author><author>Asimakopoulos, A.G.</author><author>Covaci, A.</author><author>Gevao, B.</author><author>Johnson-Restrepo, B.</author><author>Kumosani, T.A. </author><author>Malarvannan, G.</author><author>Moon, H. </author><author>Nakata, H.</author><author>Sinha, R.K. </author><author>Minh, T.B. </author><author>Kannan, K.</author></authors></contributors><titles><title>Occurrence of perchlorate in indoor dust from the United States and eleven other countries: Implications for human exposure</title><secondary-title>Environmental International </secondary-title></titles><periodical><full-title>Environmental International</full-title></periodical><pages>166-171</pages><volume>75</volume><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>].

5.5 Occupational Exposures

Exposure to perchlorate may occur at facilities where perchlorate is manufactured or used [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>]. Exposure to perchlorate in the workplace is expected to be mainly through inhalation exposure. Dermal and possibly oral exposure, through deposition of particles via mouth breathing, may also occur [ADDIN EN.CITE <EndNote><Cite><Author>Gibbs</Author><Year>1998</Year><RecNum>2046</RecNum><Displ

ayText>(Gibbs et al., 1998)</DisplayText><record><rec-number>2046</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541695841">2046</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Gibbs, J.P.</author><author>R. Ahmad</author><author>K.S. Crump</author><author>D.P. Houck</author><author>T.S. Leveille</author><author>J.E. Findley</author><author>M. Francis</author></authors></contributors><titles><title>Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function</title><secondary-title>J. Occup. Environ. Med. </secondary-title></titles><periodical><full-title>J. Occup. Environ. Med.</full-title></periodical><pages>1072-1082</pages><volume>40</volume><number>12</number><dates><year>1998</year></dates><urls></urls></record></Cite></EndNote>].

Workers at an ammonium perchlorate facility received a 35 µg/kg average absorbed dose of perchlorate over a single-shift, with a range of 0.2 to 436 µg/kg. The lifetime cumulative dose, over an average of 8.3 years, ranged from 8,000 to 88,000 µg/kg [ADDIN EN.CITE <EndNote><Cite><Author>Gibbs</Author><Year>1998</Year><RecNum>2046</RecNum><DisplayText>(Gibbs et al., 1998)</DisplayText><record><rec-number>2046</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541695841">2046</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Gibbs, J.P.</author><author>R. Ahmad</author><author>K.S. Crump</author><author>D.P. Houck</author><author>T.S. Leveille</author><author>J.E. Findley</author><author>M. Francis</author></authors></contributors><titles><title>Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function</title><secondary-title>J. Occup. Environ. Med. </secondary-title></titles><periodical><full-title>J. Occup. Environ. Med.</full-title></periodical><pages>1072-1082</pages><volume>40</volume><number>12</number><dates><year>1998</year></dates><urls></urls></record></Cite></EndNote>]. Respirable air samples at an ammonium perchlorate manufacturing facility had an average perchlorate concentration of 0.091 mg/day for workers at low dust-forming operations and an average of 0.601 and 8.591 mg/day at moderate and high dust-forming operations, respectively [ADDIN EN.CITE <EndNote><Cite><Author>Lamm</Author><Year>1999</Year><RecNum>2090</RecNum><DisplayText>(Lamm et al., 1999)</DisplayText><record><rec-number>2090</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541771491">2090</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lamm, S.H.</author><author>L.E. Braverman</author><author>F.X. Li</author><author>K. Richman</author><author>S. Pino</author><author>G. Howearth</author></authors></contributors><titles><title>Thyroid health status of ammonium perchlorate workers: A cross-sectional occupational health study</title><secondary-title>J. Occup. Environ. Med. </secondary-title></titles><periodical><full-title>J. Occup. Environ. Med.</full-title></periodical><pages>248-260</pages><volume>41</volume><number>4</number><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>].

5.6 Summary

Perchlorate exposure for the general population is mostly through the ingestion of food. Perchlorate has been detected in a wide range of food items, including fruits, vegetables, and milk and has also been detected in beer, wine, dietary supplements, and vitamins. The Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] study estimated average perchlorate exposure from food as follows: infants (6-11 months): 0.36 to 0.39 µg/kg/day; children (2 – 10 years): 0.16 to 0.48 µg/kg/day; women (25 – 70+ years): 0.09 to 0.12 µg/kg/day; men (25 – 70+ years): 0.09 to 0.13 µg/kg/day. EPA also analyzed the same data as Abt et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] and additional upper bound exposure estimates with values ranging from 0.23 µg/kg/day to 1.17 µg/kg/day when looking at the mean to 99th percentile of intake rates and considering the 95th percentile of perchlorate in food for women of child bearing age. Perchlorate has also been detected in air, with higher concentrations detected after firework displays.

6. Background on Thyroid Hormone Physiology and Connection to Neurodevelopment

In order to understand the approach the EPA has selected to derive an MCLG in accordance with SDWA, it is first necessary to have a basic understanding of thyroid physiology because perchlorate's main target is the thyroid gland. Therefore, an overview of thyroid physiology (Section [REF _Ref427059872 \r \h]), including during pregnancy (Section [REF _Ref530559488 \r \h]) is provided. This is followed by a description of thyroid pathophysiology (Section [REF _Ref486250699 \r \h]) and how thyroid hormones impact neurodevelopment (Section [REF _Ref427059920 \r \h]). These sections will provide a basis for understanding the approach to derive an MCLG presented in this document.

6.1 Overview of Thyroid Physiology

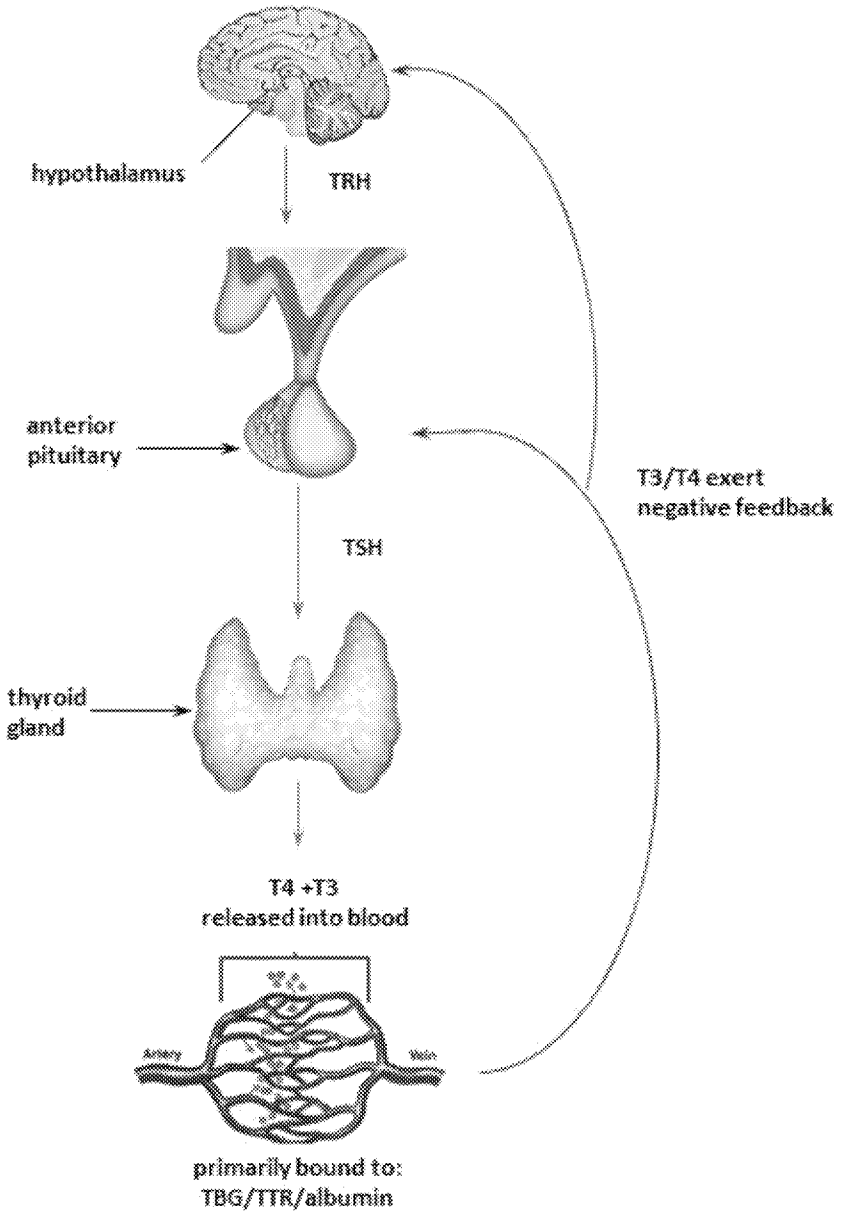
The thyroid gland is part of a "self-regulating" loop referred to as the hypothalamic-pituitary-thyroid (HPT) axis ([REF _Ref454999548 \h]), which controls metabolism, growth, and brain development and function [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2007</Year><RecNum>186</RecNum><Prefix>for review see </Prefix><DisplayText>(for review see Zoeller, Tan, & Tyl, 2007)</DisplayText><record><rec-number>186</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202457">186</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Tan, Shirlee W</author><author>Tyl, Rochelle W</author></authors></contributors><titles><title>General background on the hypothalamic-pituitary-thyroid (HPT) axis</title><secondary-title>Critical Reviews in Toxicology</secondary-title></titles><periodical><full-title>Critical reviews in toxicology</full-title></periodical><pages>11-53</pages><volume>37</volume><number>1-2</number><dates><year>2007</year></dates><isbn>1040-8444</isbn><urls></urls></record></Cite></EndNote>]. Low circulating levels of thyroid hormones stimulate hypothalamic secretion of thyrotropin-releasing hormone (TRH), which diffuses into the anterior pituitary gland and stimulates the endocrine cells within the anterior pituitary (thyrotropes) to release TSH into the circulatory system. TSH acts on the thyroid gland to stimulate iodine uptake to result in thyroid hormone production. Iodide is taken up from circulation by the NIS; serum iodide is transported into thyroid gland follicles for synthesis into the thyroid hormones T4 and to a lesser extent T3. Endocrine disruptors, such as perchlorate, could interfere with this process by directly inhibiting the uptake of iodide, thereby reducing the production of thyroid hormone.

T3 and T4 are formed when thyroglobulin (Tg; the precursor protein of T3 and T4) produced by the thyroid follicular cells is iodinated by the enzyme thyroperoxidase, and the iodinated protein is cleaved. T4 is generally thought to act as the prohormone for the more biologically active T3, which is required for normal development of the central nervous system in fetuses and in infants, as well as for ultimate skeletal development and growth. However, it should be noted that the regulatory factors that modulate the delivery of T4 to the fetus are not fully understood. Both T3 and T4 are critical determinants of metabolic function in humans of all ages. T4 and T3 are released into circulation, where they are primarily bound to the carrier proteins thyroxine-binding globulin (TBG), transthyretin (TTR), albumin, and lipoproteins [ADDIN EN.CITE ADDIN EN.CITE.DATA].

T3 and T4 in the blood that are bound to these proteins act largely as reserves because they are less readily metabolized in the liver and cannot enter cells unless in free form [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2007</Year><RecNum>186</RecNum><DisplayText>(Zoeller et al., 2007)</DisplayText><record><rec-number>186</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202457">186</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Tan, Shirlee W</author><author>Tyl, Rochelle W</author></authors></contributors><titles><title>General background on the hypothalamic-pituitary-thyroid (HPT) axis</title><secondary-title>Critical Reviews in Toxicology</secondary-title></titles><periodical><full-title>Critical reviews in toxicology</full-title></periodical><pages>11-53</pages><volume>37</volume><number>1-2</number><dates><year>2007</year></dates><isbn>1040-8444</isbn><urls></urls></record></Cite></EndNote>]. However, in their free (or unbound) states (the free or unbound states of T4 and T3 are denoted as fT4 and fT3), both are available to be transported actively into specific cells. It is important to recognize that fT4 and fT3 are in a dynamic equilibrium with protein bound T_4 and T_3, much as dissolved oxygen is in a dynamic equilibrium with that of oxygen bound to hemoglobin. T4 is transported through the cellular membrane by specific transporters and transformed by deiodinases into T3, which is then transferred to the nucleus to cause transcriptional changes. Circulating T3 is mostly derived from peripheral monodeionization of T4 [ADDIN EN.CITE <EndNote><Cite><Author>Chanoine</Author><Year>1993</Year><RecNum>343</RecNum><DisplayText>(Chanoine, Braverman, & Farwell, 1993; Peeters & Visser, 2017)</DisplayText><record><rec-number>343</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495028650">343</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chanoine, J.P. </author><author>Braverman, L.E. </author><author>Farwell, A.P. </author></authors></contributors><titles><title>The thyroid gland is a major source of circulating T3 in the rat</title><secondary-title>Journal of Clinical Investigation</secondary-title></titles><periodical><full-title>Journal of Clinical Investigation</full-title></periodical><pages>2709-2713</pages><volume>91</volume><number>6</number><dates><year>1993</year></dates><urls></urls></record></Cite><Cite><Author>Peeters</Author><Year>2017</Year><RecNum>344</RecNum><record><rec-number>344</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495029973">344</key></foreign-keys><ref-type name="Electronic Book">44</ref-type><contributors><authors><author>Peeters, R.</author><author>Visser, T.</author></authors><secondary-authors><author>De Groot, LJ</author><author>Chrousos, G </author><author>Dungan, K </author><author>et al.</author></secondary-authors></contributors><titles><title>Metabolism of thyroid hormone</title></titles><dates><year>2017</year></dates><publisher>Endotext (Internet)</publisher><urls><related-urls><url><style face="underline" font="default" size="100%">https://www.ncbi.nlm.nih.gov/books/NBK285545/</style></url></related-urls></urls></record></Cite></EndNote>]. Circulating T3 and T4 levels in an individual are maintained within a narrow range by a negative feedback loop with TSH from the pituitary and TRH from the hypothalamus (see [REF _Ref454999548 \h]) that operates around a "set point." This set point is different from individual to individual, which generates a population variance in blood levels of thyroid hormone that is considerably broader than the individual variance [ADDIN EN.CITE

<EndNote><Cite><Author>Andersen</Author><Year>2002</Year><RecNum>333</RecNum><DisplayText>(Andersen, Pedersen, Bruun, & Laurberg, 2002)</DisplayText><record><rec-number>333</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1494274249">333</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Andersen, S.</author><author>Pedersen, K.M.</author><author>Bruun, N.H.</author><author>Laurberg, P.</author></authors></contributors><titles><title>Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1068-1072</pages><volume>87</volume><number>3</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>]. Therefore, in euthyroid individuals, serum T4 and T3 fluctuate within a fairly narrow range (about 10% of the population variance), maintained by the negative feedback relationship with serum TSH from the pituitary gland. This normal variation creates a situation where single measures of free or total T4 and TSH are a somewhat imprecise measure of an individual's average T4 and TSH concentrations [ADDIN EN.CITE <EndNote><Cite><Author>Andersen</Author><Year>2002</Year><RecNum>333</RecNum><DisplayText>(Andersen et al., 2002)</DisplayText><record><rec-number>333</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1494274249">333</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Andersen, S.</author><author>Pedersen, K.M.</author><author>Bruun, N.H.</author><author>Laurberg, P.</author></authors></contributors><titles><title>Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1068-1072</pages><volume>87</volume><number>3</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>].

Figure [SEQ Figure * ARABIC]. Summary of HPT Axis Showing Negative Feedback of Increased Circulating T4 and T3 on Hypothalamus and Anterior Pituitary



It is generally thought that changes in thyroid hormone levels that occur during pregnancy operate independently of changes in the set point. For example, as the first trimester progresses, increases in human chorionic gonadotropin (hCG[7]; which operates outside the HPT axis), estrogen, and thyroxine-

[7] hCG is a hormone produced during pregnancy by cells in the placenta [ADDIN EN.CITE <EndNote><Cite><Author>American Pregnancy Association</Author><Year>2016</Year><RecNum>206</RecNum><DisplayText>(American Pregnancy Association, 2016)</DisplayText><record><rec-number>206</rec-number><foreign-

binding protein result in a higher blood concentration of total T4, making more fT4 available to the developing fetus [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2007</Year><RecNum>201</RecNum><DisplayText>(G. Morreale de Escobar, Obregón, & Escobar del Rey, 2007)</DisplayText><record><rec-number>201</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466438813">201</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, María Jesús</author><author>Escobar del Rey, F. </author></authors></contributors><titles><title>Iodine deficiency and brain development in the first half of pregnancy</title><secondary-title>Public Health Nutrition</secondary-title></titles><periodical><full-title>Public health nutrition</full-title></periodical><pages>1554-1570</pages><volume>10</volume><number>12A</number><dates><year>2007</year></dates><isbn>1475-2727</isbn><urls></urls></record></Cite></EndNote>]. Serum TSH concentrations are also mildly suppressed due to the negative feedback of this elevated serum T4 on TSH.

6.2 Thyroid Physiology in Pregnancy

In general, pregnancy requires the maternal thyroid gland to increase thyroid hormone production by around 50% [ADDIN EN.CITE <EndNote><Cite><Author>Skeaff</Author><Year>2011</Year><RecNum>180</RecNum><Prefix>for review see </Prefix><DisplayText>(for review see Skeaff, 2011)</DisplayText><record><rec-number>180</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466200929">180</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Skeaff, Sheila A</author></authors></contributors><titles><title>Iodine deficiency in pregnancy: the effect on neurodevelopment in the child</title><secondary-title>Nutrients</secondary-title></titles><periodical><full-title>Nutrients</full-title></periodical><pages>265-273</pages><volume>3</volume><number>2</number><dates><year>2011</year></dates><urls></urls></record></Cite></EndNote>] in order to provide sufficient fT4 for fetal brain development. In the first trimester of pregnancy, this increased output of thyroid hormones is, in part, due to estrogen increases during the first trimester, which increases the serum concentration of TBG, one of the main proteins to which T4 binds. The combination of increased TBG and hCG results in an increase in total T4 of about 50% over the pre-pregnancy level [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E.

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keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1467819649">206</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>American Pregnancy Association,</author></authors></contributors><titles><title>Human chorionic gonadotropin (HCG): The pregnancy hormone</title></titles><dates><year>2016</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">http://americanpregnancy.org/while-pregnant/hcg-levels/</style></url></related-urls></urls></record></Cite></EndNote>].

N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. This increase in serum total T4 also increases serum fT4 during the first trimester, although fT4 levels fall over the next two trimesters [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. The first-trimester increase in fT4 can lead in turn to a lower TSH concentration compared to the pre-pregnancy state.

Given the increased demand on the maternal thyroid in pregnancy, there is an increased demand for iodine to support additional hormone synthesis. If the maternal thyroid is fully functional, then sufficient dietary iodine intake will enable this to occur. According to the SAB, maternal hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Pages>10</Pages><DisplayText>(SAB, 2013, p. 10)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>] in the population. Although a fully functional system (i.e., in euthyroid individuals) can compensate with additional iodine consumption, hypothyroxinemic individuals are already compromised, and iodine insufficiency can exacerbate this situation, putting the fetus at risk of neurological deficits [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Maternal fT4 is particularly important in the first trimester of pregnancy because the fetal brain is solely dependent upon T4 of maternal origin during this period [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><DisplayText>(Zoeller & Rovet, 2004)</DisplayText><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet, J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>], as the fetal thyroid gland is not formed until later in development. Low maternal iodine may also impair fetal thyroid function once it begins, thereby putting the fetus at risk of developing hypothyroxinemia because it does not have enough iodine with which to synthesize its own thyroid hormone(s) ([HYPERLINK \l "_ENREF_32" \o "Dosiou, 2017 #325"]).

6.3 Thyroid Pathophysiology

Historically, the most commonly observed thyroid conditions have been goiter (i.e., enlarged thyroid gland) and congenital hypothyroidism. Hypothyroidism is defined as serum fT4 below and serum TSH above the reference range. Hypothyroidism may result from iodine insufficiency, from genetic disorders, autoimmune disease, cancer, pituitary insufficiency, or environmental factors. The most common form of adult hypothyroidism results from an autoimmune thyroiditis (Hashimoto's disease) whereby a variety of cellular and antibody-related immune processes reduce thyroid hormone production within the gland [ADDIN EN.CITE <EndNote><Cite><Author>Pyzik</Author><Year>2015</Year><RecNum>198</RecNum><Prefix>for review see </Prefix><DisplayText>(for review see Pyzik, Grywalska, Matyjaszek-Matuszek, & Roliński, 2015)</DisplayText><record><rec-number>198</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466427626">198</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pyzik, Aleksandra</author><author>Grywalska, Ewelina</author><author>Matyjaszek-Matuszek, Beata</author><author>Roliński, Jacek</author></authors></contributors><titles><title>Immune disorders in Hashimoto's Thyroiditis: What do we know so far?</title><secondary-title>Journal of Immunology Research</secondary-title></titles><periodical><full-title>Journal of immunology research</full-title></periodical><volume>2015</volume><dates><year>2015</year></dates><isbn>2314-8861</isbn><urls></urls></record></Cite></EndNote>]. Both post-partum thyroiditis and subacute lymphocytic (or silent) thyroiditis are considered subtypes of this disorder. Post-partum thyroiditis can occur in up to 5% of women and can involve periods of hyper- and hypo-thyroid activity [ADDIN EN.CITE <EndNote><Cite><Author>Akamizu</Author><Year>2015</Year><RecNum>169</RecNum><Prefix>for review see </Prefix><DisplayText>(for review see Akamizu & Amino, 2015; E.N. Pearce, 2015)</DisplayText><record><rec-number>169</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466199550">169</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Akamizu, T.</author><author>Amino, N.</author></authors><secondary-authors><author>De Groot, L.J.</author><author>Chrouos, G.</author><author>Dungan, K.</author><author>Feingold, K.R.</author><author>Grossman, A.</author><author>Hershman, J.M.</author><author>Koch, C. </author><author>Korbonits, M.</author><author>McLachlan, R. </author><author>New, M. </author><author>Purnell,

J.</author><author>Rebar, R. </author><author>Singer, F. </author><author>Vinik, A. </author></secondary-authors></contributors><titles><title>Hashimoto's Thyroiditis</title><secondary-title>Endotext </secondary-title></titles><dates><year>2015</year></dates><pub-location>South Dartmouth, MA</pub-location><publisher>MDText.com, Inc.</publisher><urls></urls></record></Cite><Cite><Author>Pearce</Author><Year>2015</Year><RecNum>179</RecNum><record><rec-number>179</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466200902">179</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pearce, E.N.</author></authors></contributors><titles><title>Thyroid disorders during pregnancy and postpartum</title><secondary-title>Best Practice & Research Clinical Obstetrics & Gynaecology</secondary-title></titles><periodical><full-title>Best Practice & Research Clinical Obstetrics & Gynaecology</full-title></periodical><pages>700-706</pages><volume>29</volume><number>5</number><dates><year>2015</year></dates><isbn>1521-6934</isbn><urls></urls></record></Cite></EndNote>]. Generally, the condition will resolve itself; however, as many as 20% of cases may lead to permanent hypothyroidism.

Hashimoto's disease increases the risk of hypothyroidism, including both subclinical and overt hypothyroidism. Subclinical hypothyroidism is defined by only elevated (or outside the reference range) TSH concentrations, with serum T3 and T4 concentrations that remain within the population reference range, while overt hypothyroidism is defined by elevated serum TSH concentrations concurrent with decreased (or outside the reference range) serum T3 and T4 concentrations. Subclinical hypothyroidism has the potential to progress to overt hypothyroidism over time; thus, it requires serum thyroid function test monitoring. Other related autoimmune hypothyroid conditions include primary thyroid atrophy (Ord's disease), which is characterized by thyroid atrophy through invasion by T-lymphocytes, and is likely part of the continuum of hypothyroid conditions, rather than a separate disorder from Hashimoto's disease [ADDIN EN.CITE <EndNote><Cite><Author>Carlé</Author><Year>2009</Year><RecNum>172</RecNum><DisplayText>(Carlé et al., 2009)</DisplayText><record><rec-number>172</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466200413">172</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Carlé, Allan</author><author>Pedersen, Inge Bulow</author><author>Knudsen, Nils</author><author>Perrild, Hans</author><author>Ovesen, Lars</author><author>Jørgensen, Torben</author><author>Laurberg, Peter</author></authors></contributors><titles><title>Thyroid volume in hypothyroidism due to autoimmune disease follows a unimodal distribution: evidence against primary thyroid atrophy and autoimmune thyroiditis being distinct diseases</title><secondary-title>The Journal of Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>The Journal of Clinical Endocrinology & Metabolism</full-title></periodical><pages>833-839</pages><volume>94</volume><number>3</number><dates><year>2009</year></dates><isbn>0021-972X</isbn><urls></urls></record></Cite></EndNote>]. Viral or other infections can result in the painful condition of subacute granulomatous thyroiditis. This condition, like post-partum thyroiditis, is generally transient and requires only beta-blocker and non-steroidal anti-inflammatory drugs (NSAIDs) or steroid treatment to resolve. Although not common, pituitary disorders or tumors can also result in reduced thyroid function through reduction in TSH output.

Thyroid peroxidase antibodies (also referred to as anti-thyroid peroxidase antibodies or TPO Abs) are a marker for thyroid autoimmunity, a condition in which a person's immune system antibodies mistakenly target parts of the thyroid gland or thyroid proteins. Thyroid autoimmunity leads to chronic inflammation of the thyroid, can cause tissue damage, and may disrupt thyroid function. The TPO Abs work against thyroid peroxidase, which is an enzyme involved in the synthesis of thyroid hormones [ADDIN EN.CITE <EndNote><Cite><Author>Braverman</Author><Year>2004</Year><RecNum>1991</RecNum><DisplayText>(L. Braverman & Utiger, 2004)</DisplayText><record><rec-number>1991</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1525112324">1991</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Braverman, L </author><author>Utiger, R.S.</author></authors><secondary-authors><author>Taurog, A.</author></secondary-authors></contributors><titles><title>Hormone synthesis: Thyroid iodine metabolism.</title><secondary-title>The Thyroid: A Fundamental and Clinical Text.</secondary-title></titles><pages>61-85</pages><dates><year>2004</year></dates><pub-location>Philadelphia</pub-location><publisher>Lippincott-Raven</publisher><urls></urls></record></Cite></EndNote>].

6.4 Physiologic Connection between Thyroid Hormone Levels and Neurodevelopment

The profound effects of thyroid deficiencies during development were first documented in children with congenital hypothyroidism by Paracelsus [ADDIN EN.CITE <EndNote><Cite><Author>Cranefield</Author><Year>1963</Year><RecNum>1892</RecNum><DisplayText>(Cranefield & Federn, 1963)</DisplayText><record><rec-number>1892</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497969366">1892</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Cranefield, P.</author><author>Federn, W.</author></authors></contributors><titles><title>Paracelsus on goiter and cretinism: A translation and discussion of "De Struma, Vulgo Der Kropf"</title><secondary-title>Bulletin of the History of Medicine</secondary-title></titles><periodical><full-title>Bulletin of the History of Medicine</full-title></periodical><pages>463-471</pages><volume>37</volume><dates><year>1963</year></dates><urls></urls></record></Cite></EndNote>]. Modern studies demonstrate that unless treated, children with congenital hypothyroidism will suffer from problems associated with somatic growth and an array of visuomotor and neurocognitive deficits. Aberrant patterns of growth, development, and organization of the cortex, cerebellum, hippocampus, basal ganglia, and brain stem can all result from reduced thyroid hormone exposure during development [ADDIN EN.CITE <EndNote><Cite><Author>Williams</Author><Year>2008</Year><RecNum>193</RecNum><DisplayText>(Williams, 2008; Zoeller & Rovet, 2004)</DisplayText><record><rec-number>193</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202836">193</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, GR</author></authors></contributors><titles><title>Neurodevelopmental and neurophysiological actions of thyroid hormone</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>784-

794</pages><volume>20</volume><number>6</number><dates><year>2008</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet, J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>].

Thyroid hormones are essential for the development and differentiation of the developing brain. The brain and spinal cord begin development in the first half of the first trimester. Free T4 can reach the brain, though the exact mechanism by which is does so is actively being researched [ADDIN EN.CITE <EndNote><Cite><Author>Wirth</Author><Year>2014</Year><RecNum>2233</RecNum><Prefix>e.g.`, </Prefix><DisplayText>(e.g., Wirth, Schweizer, & Kohrle, 2014)</DisplayText><record><rec-number>2233</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543328103">2233</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Wirth, E.K.</author><author>Schweizer, U.</author><author>Kohrle, J.</author></authors></contributors><titles><title>Transport of thyroid hormone in brain</title><secondary-title>Frontiers in Endocrinology</secondary-title></titles><periodical><full-title>Frontiers in endocrinology</full-title></periodical><pages>1-7</pages><volume>5</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. However, once present in the brain, T4 is converted to T3 by the developing glial cells and then transported to neurons. T3 then interacts with nuclear receptors to tightly regulate gene expression so that neurogenesis, synaptogenesis, neuronal migration, cell differentiation, and myelination are developmentally appropriate. Deficiencies in thyroid hormones through iodine deficiency, congenital hypothyroidism, or maternal hypothyroidism/hypothyroxinemia can result in neurological impairments and intellectual deficits [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2000</Year><RecNum>1885</RecNum><DisplayText>(G. Morreale de Escobar, Obregón, & Escobar del Rey, 2000)</DisplayText><record><rec-number>1885</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1496433675">1885</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F.</author></authors></contributors><titles><title>Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia?</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>3975-3987</pages><volume>85</volume><number>11</number><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>].

The fetal thyroid gland first begins to concentrate iodide at about 11–12 weeks and begins significant contribution to fetal development around 16 weeks. However, the developing fetus still relies on some supply of maternal thyroid hormones until birth [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(G. Morreale de Escobar, Obregón, & Escobar del Rey, 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437077734">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>]. The fetal thyroid is not fully mature until birth, so premature birth can also be associated with low thyroid hormone concentrations. Thus, alterations in thyroid hormone levels can impact brain development in a variety of ways depending on when the alteration occurs and for how long.

For example, early in brain development, fT4 deficiency can affect neuronal cell proliferation and cell migration in the hippocampus (essential for learning and memory, cognitive function), the cerebral cortex (essential for executive function, cognitive function), and the medial ganglionic eminence (transitory development structure responsible for guiding axonal migration) [ADDIN EN.CITE <EndNote><Cite><Author>Williams</Author><Year>2008</Year><RecNum>193</RecNum><DisplayText>(Williams, 2008)</DisplayText><record><rec-number>193</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202836">193</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, GR</author></authors></contributors><titles><title>Neurodevelopmental and neurophysiological actions of thyroid hormone</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>784-794</pages><volume>20</volume><number>6</number><dates><year>2008</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>]. Maternal hypothyroidism or hypothyroxinemia at these early stages may result in problems with gross motor skills and visual attention and processing [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><DisplayText>(Zoeller & Rovet, 2004)</DisplayText><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet, J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of

neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>]. As the first trimester progresses, increases in hCG result in a higher production of T4 [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2007</Year><RecNum>201</RecNum><DisplayText>(G. Morreale de Escobar et al., 2007)</DisplayText><record><rec-number>201</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466438813">201</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, María Jesús</author><author>Escobar del Rey, F. </author></authors></contributors><titles><title>Iodine deficiency and brain development in the first half of pregnancy</title><secondary-title>Public Health Nutrition</secondary-title></titles><periodical><full-title>Public health nutrition</full-title></periodical><pages>1554-1570</pages><volume>10</volume><number>12A</number><dates><year>2007</year></dates><isbn>1475-2727</isbn><urls></urls></record></Cite></EndNote>]. In addition, serum TBG increases during the first trimester, remaining elevated throughout pregnancy because estrogen increases the glycosylation of TBG, increasing its serum half-life. In the fetus this period also corresponds to neurogenesis in the midbrain and cortex, neuronal migration into the cortex, deiodinase activity for conversion of T4 to T3, and presence of nuclear thyroid receptors in the brain [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(G. Morreale de Escobar et al., 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437077734">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>].

Higher levels of maternal fT4 throughout pregnancy allow for normal neuron and glial cell migration and differentiation, axonal growth, dendritic branching, neurogenesis, and synaptogenesis to occur [ADDIN EN.CITE <EndNote><Cite><Author>Williams</Author><Year>2008</Year><RecNum>193</RecNum><DisplayText>(Williams, 2008)</DisplayText><record><rec-number>193</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202836">193</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, GR</author></authors></contributors><titles><title>Neurodevelopmental and neurophysiological actions of thyroid hormone</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-

title></periodical><pages>784-794</pages><volume>20</volume><number>6</number><dates><year>2008</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>]. The complex interconnectedness of brain regions required for normal function could be impaired by effects on all of these processes simultaneously or in sequence, and across multiple brain regions. Maternal thyroid deficiencies during these processes further affect visual processing, development of fine motor skills, IQ, and selective learning problems [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><DisplayText>(Zoeller & Rovet, 2004; Zoeller et al., 2007)</DisplayText><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet, J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite><Cite><Author>Zoeller</Author><Year>2007</Year><RecNum>186</RecNum><record><rec-number>186</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202457">186</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Tan, Shirlee W</author><author>Tyl, Rochelle W</author></authors></contributors><titles><title>General background on the hypothalamic-pituitary-thyroid (HPT) axis</title><secondary-title>Critical Reviews in Toxicology</secondary-title></titles><periodical><full-title>Critical reviews in toxicology</full-title></periodical><pages>11-53</pages><volume>37</volume><number>1-2</number><dates><year>2007</year></dates><isbn>1040-8444</isbn><urls></urls></record></Cite></EndNote>]. Additionally, concern is emerging that there may be adverse effects associated with fT4 levels above the normal range (Korevaar et al., 2016).

Additionally, humans continue to undergo considerable post-natal brain development well through puberty and into early adulthood. A properly functioning HPT is necessary for proper neurologic development at this stage [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><DisplayText>(Zoeller & Rovet, 2004)</DisplayText><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet, J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>]. This is particularly true in the

hippocampus, which is considered to have a relatively high degree of neuroplasticity in humans and undergoes considerable adult neurogenesis. How the behavioral and cognitive deficits associated with subclinical hypothyroidism and hypothyroxinemia are manifested within the brain is a research area where further evaluation is needed.

7. Overview of Perchlorate's Impact on the Thyroid

As stated previously, the main target for perchlorate's toxicity is the thyroid gland. In this section the mode of action for perchlorate is discussed along with an overview of studies that have evaluated perchlorate's impact on the human thyroid.

7.1 Mode of Action

In 2005, the NRC proposed a mode of action for perchlorate. [REF _Ref455000569 \h] is a reproduction of this mode of action modified to include hypothyroxinemia. Evaluating hypothyroxinemia as a result of perchlorate exposure is the mode of action that the SAB recommended the EPA utilize in evaluating the MCLG for perchlorate. [REF _Ref455000569 \h] begins with exposure to perchlorate, which then leads to perchlorate in the bloodstream, followed by the inhibition of iodide uptake in the thyroid. The NRC concluded that these steps have all been observed in humans, and any subsequent steps or results are biologically possible, but have not been clearly demonstrated in humans. However, since the 2005 NRC report was published, several epidemiological studies have shown perchlorate exposure to be associated with changes in serum thyroid hormone levels [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Furthermore, Taylor et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Taylor</Author><Year>2014</Year><RecNum>2032</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>2032</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541511371">2032</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Taylor, P.</author><author>Okosieme, O. E.</author><author>Murphy, R.</author><author>Hales, C.</author><author>Chiusano, E.</author><author>Maina, A., . . .</author><author>Paradice, R.</author></authors></contributors><titles><title>Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring: data from the controlled antenatal thyroid study</title><secondary-title>The Journal of Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>The Journal of Clinical Endocrinology & Metabolism</full-title></periodical><pages>8</pages><volume>99</volume><section>4291</section><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>] demonstrated an association between high maternal perchlorate exposure and risk of low IQ in offspring.

In their review, NRC deemed the inhibition of iodide uptake in the thyroid to be a non-adverse effect, and concluded that the body's compensatory mechanisms would keep thyroid hormone levels within the population reference range [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-

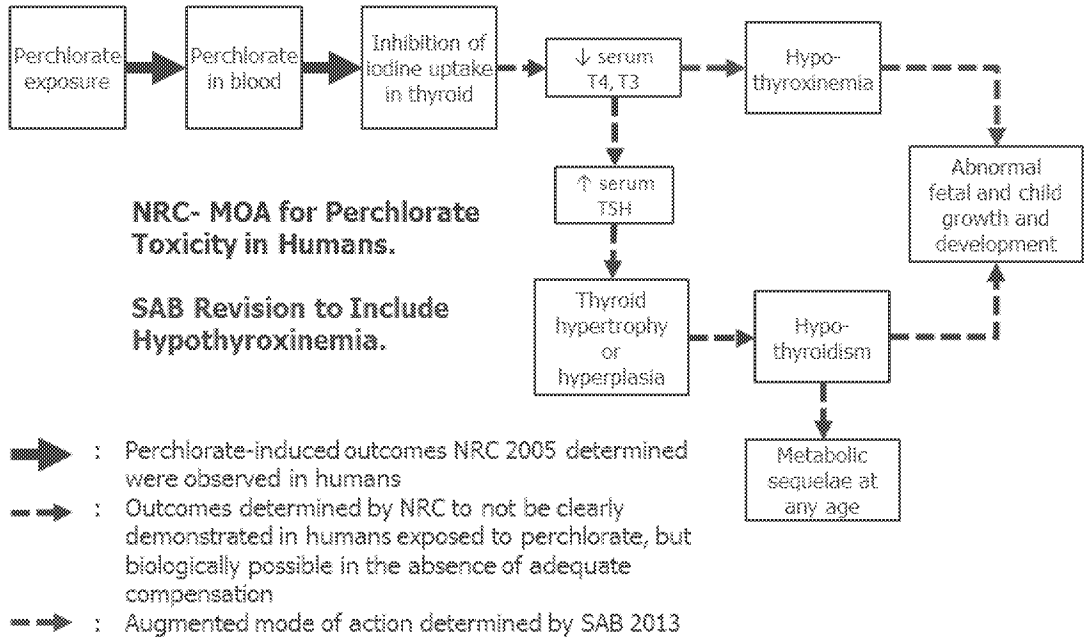
date>National Research Council</modified-date></record></Cite></EndNote>]. However, concerns have been raised regarding this conclusion given the lack of empirical evidence provided to support it [ADDIN EN.CITE <EndNote><Cite><Author>Ginsberg</Author><Year>2007</Year><RecNum>345</RecNum><DisplayText>(Ginsberg, Hattis, Zoeller, & Rice, 2007)</DisplayText><record><rec-number>345</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495122121">345</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ginsberg, G.</author><author>Hattis, R.</author><author>Zoeller, R Thomas</author><author>Rice, D.C.</author></authors></contributors><titles><title>Evaluation of the U.S. EPA/OSWER Preliminary Remediation Goal for Perchlorate in Groundwater: Focus on Exposure to Nursing Infants</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><volume>115</volume><number>3</number><section>361</section><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>]. The NRC did list subsequent biologically plausible steps, downstream from iodine uptake inhibition, that include the following: altered thyroid hormone levels (e.g., decreased T3 and T4, increased TSH; which has now been demonstrated in the epidemiologic literature), growth of the thyroid gland (e.g., thyroid hypertrophy and hyperplasia), and hypothyroidism.

Hypothyroidism, deemed by the NRC to be the first adverse effect, could lead to abnormal fetal and child growth development, as well as metabolic disorders at all ages. Given the importance of a properly functioning thyroid for fetal and child growth [ADDIN EN.CITE <EndNote><Cite><Author>Forhead</Author><Year>2014</Year><RecNum>1890</RecNum><DisplayText>(Forhead & Fowden, 2014)</DisplayText><record><rec-number>1890</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497623515">1890</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Forhead, A J</author><author>Fowden, A L</author></authors></contributors><titles><title>Thyroid hormones in fetal growth and prepartum maturation</title><secondary-title>Journal of Endocrinology</secondary-title></titles><periodical><full-title>Journal of Endocrinology</full-title></periodical><pages>R87-R103</pages><volume>221</volume><number>3</number><dates><year>2014</year><pub-dates><date>June 1, 2014</date></pub-dates></dates><urls><related-urls><url>http://joe.endocrinology-journals.org/content/221/3/R87.abstract</url></related-urls></urls><electronic-resource-num>10.1530/joe-14-0025</electronic-resource-num></record></Cite></EndNote>], both hypothyroidism and hypothyroxinemia (low fT4 with TSH in the reference range) may also be associated with abnormal fetal and child growth.

In the SAB report on approaches to derive an MCLG for perchlorate, the SAB indicates that "the mode of action of perchlorate toxicity is well understood" [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Pages>2</Pages><DisplayText>(SAB, 2013, p. 2)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level

goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>]. The SAB finds that "hypothyroxinemia (i.e., low levels of thyroid hormone) is a more appropriate indicator of the potential adverse health effects than the more pronounced decreases in thyroid hormone associated with hypothyroidism" ([ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><DisplayText>(SAB, 2013)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>], p. 2). Moreover, the "sensitive populations EPA should consider for exposure to perchlorate are the fetuses of hypothyroxinemic pregnant women" [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Pages>2</Pages><DisplayText>(SAB, 2013, p. 2)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>].

Figure [SEQ Figure * ARABIC]. Modified Representation of NRC's Suggested Mode of Action for Perchlorate Toxicity in Humans Indicating First Adverse Effect in the Continuum of Perchlorate Exposure to Effect, Revised to Include Hypothyroxinemia as recommended by the SAB



Source: Adapted from NRC [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>National Research Council (NRC)</Author><Year>2005</Year><RecNum>116</RecNum><Suffix>`, Figure 5-2 (modified)`, Figure 5-2 (modified)`, Figure 5-2 (modified)`, Figure 5-2 (modified)</Suffix><DisplayText>(2005, Figure 5-2 (modified), Figure 5-2 (modified), Figure 5-2 (modified), Figure 5-2 (modified))</DisplayText><record><rec-number>116</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914312">116</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>National Research Council (NRC),</author></authors></contributors><titles><title>Health implications of perchlorate exposure</title></titles><dates><year>2005</year></dates><pub-location>Washington, D.C.</pub-location><publisher>The National Academies Press</publisher><urls></urls></record></Cite></EndNote>].
Notes: Solid arrows represent outcomes that the NRC [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>National Research Council (NRC)</Author><Year>2005</Year><RecNum>116</RecNum><DisplayText>(2005)</DisplayText><record><rec-number>116</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914312">116</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>National Research Council (NRC),</author></authors></contributors><titles><title>Health implications of perchlorate exposure</title></titles><dates><year>2005</year></dates><pub-location>Washington, D.C.</pub-location><publisher>The National Academies Press</publisher><urls></urls></record></Cite></EndNote>] determined were observed in humans during perchlorate exposure. Black dashed arrows represent outcomes determined by the NRC [ADDIN EN.CITE <EndNote><Cite ExcludeYear="1"><Author>National Research Council (NRC)</Author><Year>2005</Year><RecNum>116</RecNum><DisplayText>(National Research Council (NRC))</DisplayText><record><rec-number>116</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914312">116</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>National Research Council (NRC),</author></authors></contributors><titles><title>Health implications of perchlorate exposure</title></titles><dates><year>2005</year></dates><pub-location>Washington, D.C.</pub-location><publisher>The National Academies Press</publisher><urls></urls></record></Cite></EndNote>] to have not been clearly demonstrated in humans exposed to perchlorate, but that are biologically possible in the absence of adequate compensation. Blue dashed arrows represent the augmented mode of action from the SAB.

7.2 Overview of Evidence Evaluating Perchlorate's Impact on the Human Thyroid

The proposed mode of action is informed by the knowledge developed from decades of research on perchlorate's impact on the thyroid gland conducted both through clinical trials and, more recently, through environmental epidemiological studies. Given the abundance of human data and the differences in serum binding and clearance rates and differences in thyroid stimulation by a placental hormone in pregnant women between rats and humans (NRC, 2005) the Agency does not summarize the toxicological literature in this section. Instead an overview of clinical studies and environmental epidemiological studies, evaluating the association between perchlorate exposure (measured as either a given dose or through biomonitoring) and impacts on measures of thyroid homeostasis are summarized.

7.2.1 Clinical Studies

Understanding perchlorate's impact on the thyroid in a clinical setting has occurred since at least the 1950s. For example, Stanbury and Wyngaarden [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Stanbury</Author><Year>1952</Year><RecNum>2192</RecNum><DisplayText>(1952)</DisplayText><record><rec-number>2192</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541782564">2192</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Stanbury, J.B. </author><author>J.B. Wyngaarden</author></authors></contributors><titles><title>Effect of perchlorate on the human thyroid gland</title><secondary-title>Metabolism</secondary-title></titles><periodical><full-title>Metabolism</full-title><abbr-1>Metabolism</abbr-1></periodical><pages>533-539</pages><volume>1</volume><number>6</number><dates><year>1952</year></dates><urls></urls></record></Cite></EndNote>], Godley and Stanbury [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>A.F.</Author><Year>1954</Year><RecNum>2113</RecNum><DisplayText>(1954)</DisplayText><record><rec-number>2113</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541774730">2113</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Godley, A.F. </author><author>Stanbury, J.B.</author></authors></contributors><titles><title>Preliminary experience in the treatment of hyperthyroidism with potassium perchlorate. </title><secondary-title>J. Clin. Endocrinol. </secondary-title></titles><periodical><full-title>J. Clin. Endocrinol.</full-title></periodical><pages>70-78</pages><volume>14</volume><dates><year>1954</year></dates><urls></urls></record></Cite></EndNote>], and Burgi et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Bürgi</Author><Year>1974</Year><RecNum>2115</RecNum><DisplayText>(1974)</DisplayText><record><rec-number>2115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541774836">2115</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bürgi, H.</author><author>M. Benguerel</author><author>J. Knopp</author><author>H. Kohler</author><author>H. Studer</author></authors></contributors><titles><title>Influence of perchlorate on the secretion of non-thyroxine iodine by the normal human thyroid gland</title><secondary-title>Eur. J. Clin. Invest. </secondary-title></titles><periodical><full-title>Eur. J. Clin. Invest.</full-title></periodical><pages>65-

69</pages><volume>4</volume><dates><year>1974</year></dates><urls></urls></record></Cite></EndNote>] all noted perchlorate's impact on reducing iodine uptake by the thyroid gland.

In 1992, Brabant et al. used perchlorate to study changes in temporal patterns of TSH response to a decrease in iodine supply. Specifically, in this study the authors treated 5 healthy male volunteers (aged 25-28) with 200 µg/day of iodine for 4 weeks. This was then followed by treatment of 300 mg of perchlorate three times per day over a four week period to induce an iodine depleted state in the study participants. As anticipated, the authors did see a significant decrease in iodine uptake with the perchlorate treatment. Further, the authors also noted that 24-hour mean serum TSH, TSH per pulse and serum fT4 levels were significantly decreased during treatment period. The authors did not observe any change in thyroid volume and total serum T3, T4 or fT3.

In another study, Lawrence et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lawrence</Author><Year>2000</Year><RecNum>228</RecNum><DisplayText>(2000)</DisplayText><record><rec-number>228</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468246590">228</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lawrence, J.E.</author><author>S.H. Lamm</author><author>S. Pino</author><author>K. Richman</author><author>Braverman, L</author></authors></contributors><titles><title>The effect of short-term low-dose perchlorate on various aspects of thyroid function</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>659-663</pages><volume>10</volume><number>8</number><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>] gave nine healthy men (ages 22-30 years old) 10 mg of potassium perchlorate (about 0.10 mg/kg/day perchlorate for a 70 kg person) in one liter of water daily for 14 days. Their serum perchlorate concentrations averaged 0.6 µg/mL, and the average urinary perchlorate excretion was 7.7 mg per day. There were no changes in serum T4, T3, or TSH concentrations during the 14-day period of perchlorate ingestion. A highly significant decrease in the thyroid ^{123}I uptake was observed at 14 days (38 percent below baseline) and a significant increase was observed 14 days after the treatment was stopped. Dietary iodine intakes were relatively high, as indicated by baseline urinary iodine levels of 254 µg/24 hr; 14 days of perchlorate exposure increased urinary iodide to 385 µg/24 hr, whereas after 14 days of recovery, urine iodine excretion was 208 µg/24 hr. The high dietary iodine intake in this study may have reduced the impact of perchlorate on the thyroid. However, the decreased iodine uptake during perchlorate administration, followed by an increase, indicates that total thyroidal colloid stores were being depleted, and replenished after treatment ceased.

In a follow-up study, the same investigators administered 3 mg of perchlorate as the potassium salt daily (perchlorate at about 0.04 mg/kg/day for a 70-kg person) to eight healthy men (ages not given) for 14 days [ADDIN EN.CITE <EndNote><Cite><Author>Lawrence</Author><Year>2001</Year><RecNum>292</RecNum><DisplayText>(Lawrence, Lamm, & Braverman, 2001)</DisplayText><record><rec-number>292</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1470160607">292</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lawrence, J.E.</author><author>Lamm, Steven</author><author>Braverman, L</author></authors></contributors><titles><title>Low dose perchlorate (3 mg daily) and thyroid

function</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>295-295</pages><volume>11</volume><number>3</number><dates><year>2001</year></dates><isbn>1050-7256</isbn><urls></urls></record></Cite></EndNote>]. The mean 24-hr thyroid uptake of radioactive iodine was 16.1% at baseline and 14.5% during perchlorate ingestion, and the mean 8-hr uptake values were 13.8% and 11.8%, respectively; neither change was statistically significant. There were no changes in serum T4, T3, or TSH concentrations. However, in evaluating the results of the shorter term (e.g., 2-week) studies one should consider that the adult euthyroid human thyroid contains several months of T4 stored in the colloid, it is not expected that a 2-week study would result in a change in thyroid status (Dunn & Dunn, 2000, and Brabant et al., 1992, both as cited in Greer et al., 2002).

Further supporting evidence that perchlorate inhibits iodine uptake comes from Greer et al. (2002). As previously described the NRC selected this as the critical study in their derivation of the RfD. In Greer et al. (2002) 37 subjects were recruited in an attempt to analyze the effects associated with perchlorate exposure from drinking water, including altered thyroid function that was measured by the inhibition of RAIU. The test subjects were assigned to one of two groups, which followed similar study protocols. The first group, Group A, consisted of 12 male and 12 female subjects. These 24 subjects were assigned to one of three dose groups of 0.02, 0.1 or 0.5 mg/kg-day of perchlorate. 4 individuals of each sex were in each dose group.

The other study group, Group B, contained the remaining 13 subjects of which 9 were female and 4 were male. In the uptake study, 6 females and 1 male were dosed with 0.007 mg/kg-day of perchlorate and the other 6 subjects were dosed with 0.02, 0.1 or 0.5 mg/kg-day of perchlorate (one male and one female were in each dose group). An overview of the number of subjects in Groups A and B can be seen in [REF _Ref293306990 \h * MERGEFORMAT].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Summary of Number of Subjects in Each of the Dose Groups from Greer et al. (2002) by Study Protocol

Dose Group (mg/kg-day)	Group A			Group B		
	N			N		
	Male	Female	Total	Male	Female	Total
0.007	0	0	0	1	6	7
0.02	4	4	8	1	1	2
0.1	4	4	8	1	1	2
0.5	4	4	8	1	1	2
Total	12	12	24	4	9	13
	37					

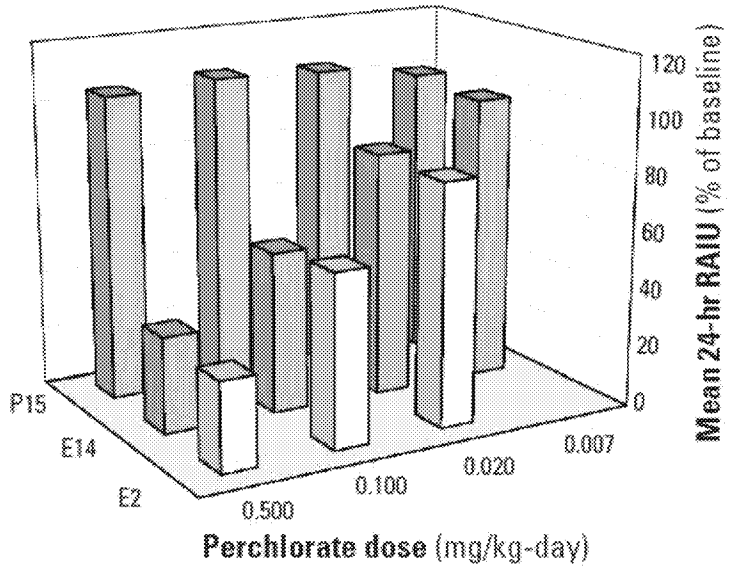
Each subject drank 400 mL of water containing their specified dose of perchlorate in 100 mL increments. This was done for 14 consecutive days. For the Group A subjects, ^{123}I was ingested four times: (1) the baseline visit (one day before exposure began); (2) the second day of exposure (E2); (3)

the 14th day of exposure (E14) and; (4) the post-exposure day 15 (P15). RAIU measurements were taken eight hours after ingestion on the day of ^{123}I ingestion, and then again 24 hours after ingestion.

For the Group B subjects ^{123}I was only ingested three times: (1) the baseline visit; (2) E14 and; (3) P15. After the baseline visit and E14, RAIU measurements were taken eight hours after ingestion on the day of ^{123}I ingestion, and then again 24 hours later. P15 RAIU measurements were completed only at 09:00 on the morning following ^{123}I ingestion for the uptake study subjects.

A strong correlation was observed between the eight- and 24-hour RAIU measurements over all of the dose groups and measurement days. The authors found no differences between the E2 and E14 RAIU measurements (the dose-response was a negative linear function of the logarithm of dose for the E2 and E24 measurements). Additionally, no difference was found between sexes. [REF _Ref293307032 \h * MERGEFORMAT] presents the percent of RAIU change 24 hours after ^{123}I ingestion for each exposure day, compared to the baseline RAIU measure. No impact was seen on thyroid hormone levels.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. The Mean 24-hour RAIU (09:00, Day After ^{123}I Ingestion) Relative to Baseline for Each Dose Group on E2, E14, and P15



Source: Greer et al. (2002) Figure 3.

Greer et al. (2002) found the "lowest dose producing no statistically significant inhibition of RAIU uptake was 0.007 mg/kg-day." In this lowest dose group on E14, RAIU was 98.2% of the baseline with a standard deviation of 8.3%, indicating the variability seen within Group B. The dose group of 0.007 mg/kg-day, was deemed to be the NOEL for inhibition of RAIU. Given this was the lowest dose administered to study subjects, Greer derived an estimate for a "true no-effect level" and came up with 5.2 and 6.4 µg/kg-day for the eight- and 24-hour uptake measurements on E14, respectively. The values Greer et al. (2002) calculated to be the "true no-effect level" doses would be ingested by

an adult (assuming default BW and drinking water ingestions assumptions[8]) if the drinking water supply contained perchlorate at concentrations of approximately 180 µg/L and 220 µg/L. Regarding the P15 measurements, the RAIU was not significantly different from the baseline, indicating that 15 days after perchlorate exposure ended, there were no lasting effects of iodide uptake inhibition (IUI). No data on subject iodine status was obtained in Greer et al. (2002), which is important given perchlorate's impact is greatest on those with lower iodine intake.

The lower dose studies summarized above are all short term studies that observed decreases in iodine uptake by the thyroid with perchlorate treatment. In these studies no impacts on thyroid hormone levels were noted. Given the several months of T4 stored in the thyroid impacts on hormone levels are not expected. There is one small (n = 13), longer-term clinical trial with six-months of perchlorate ingestion at rates of 0.5 or 3 mg of perchlorate ingestion per day (Braverman et al., 2006). No changes in thyroid function, including in iodine uptake, were observed in this study. However, urinary iodide levels among participants in this study were considerably higher than the national average (mean 257.8 µg/total volume before 0.5 mg dose of perchlorate; mean 311.5 µg/total volume before 3 mg dose of perchlorate), which could be protective. Subsequently, the results of this study are consistent with evidence that healthy adults may be protected against the thyroid hormone changes associated with perchlorate exposures given adequate dietary iodine intake [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>].

Overall, the clinical studies on perchlorate on the thyroid have shown that in healthy volunteers perchlorate has impacted iodine uptake by the thyroid (Lawrence et al., 2000; Lawrence et al., 2001; Greer et al., 2005). Additionally, in study participants with high iodine intake levels there may be a protective effect against the iodine uptake inhibition caused by perchlorate ingestion (Braverman et al. 2006). None of the clinical trials, with the exception of the higher dose study of Brabant et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Brabant</Author><Year>1992</Year><RecNum>2104</RecNum><DisplayText>(1992)</DisplayText><record><rec-number>2104</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541773981">2104</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Brabant, G.P.</author><author>P. Bergmann</author><author>C.M. Kirsch</author><author>J. Kohrle</author><author>R.D. Hesch</author><author>A. von zur Muhlen</author></authors></contributors><titles><title>Early adaptation of thyrotropin and thyroglobulin secretion to experimentally decreased iodide supply in

[8] Default BW is 70 kg, and default ingestion rate is 2 L/day.

man</title><secondary-title>Metabolism</secondary-title></titles><periodical><full-title>Metabolism</full-title><abbr-1>Metabolism</abbr-1></periodical><pages>1093-1096</pages><volume>41</volume><number>10</number><dates><year>1992</year></dates><urls></urls></record></Cite></EndNote>] demonstrated an impact of perchlorate on thyroid hormone levels. However, it is unlikely healthy, euthyroid individuals with adequate iodine intake will experience changes in thyroid hormone levels in the short-term studies. In the longer term study (Braverman et al., 2006) in individuals with high iodine impact, no impact on the thyroid was seen.

7.2.2 Environmental Epidemiological Studies – General Population

In addition to what is seen in clinical exposure studies, there are several more recent epidemiological studies. Specifically, several studies have been published in the last twelve years which use data from NHANES and have found an association between low level perchlorate exposure (measured as urinary perchlorate) in the U.S. and thyroid hormone levels. This association is most noticeable in individuals with low urinary iodine levels and co-exposures to other goitrogens[9].

The first such study was Blount et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Blount</Author><Year>2006</Year><RecNum>224</RecNum><DisplayText>(2006)</DisplayText><record><rec-number>224</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468246110">224</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Blount, B. C.</author><author>Pirkle, J. L.</author><author>Osterloh, J. D.</author><author>Valentin-Blasini, L.</author><author>Caldwell, K. L.</author></authors></contributors><titles><title>Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>1865-71</pages><volume>114</volume><number>12</number><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>] who examined the relationship between urinary levels of perchlorate and serum levels of TSH and total T4 in 2,299 men and women (ages 12 years and older), who participated in CDC's 2001-2002 NHANES.[10] Blount et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Blount</Author><Year>2006</Year><RecNum>224</RecNum><DisplayText>(2006)</DisplayText><record><rec-number>224</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468246110">224</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Blount, B. C.</author><author>Pirkle, J. L.</author><author>Osterloh, J. D.</author><author>Valentin-Blasini, L.</author><author>Caldwell, K. L.</author></authors></contributors><titles><title>Urinary

[9] Substances that disrupt the production of thyroid hormones by interfering with iodine uptake in the thyroid gland.

[10] While CDC researchers measured urinary perchlorate concentration for 2,820 NHANES participants, TSH and total T4 serum levels were only available for 2,299 of these participants.

perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>1865-71</pages><volume>114</volume><number>12</number><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>] evaluated perchlorate along with covariates known or likely to be associated with T4 or TSH levels to assess the relationship between perchlorate and these hormones, and the influence of other factors on this relationship. The study found that perchlorate was a significant predictor of thyroid hormones in women, but not men. The 1,111 women were further analyzed after being divided into two categories, higher-iodine and lower-iodine, using a cut point of 100 µg/L of urinary iodine, based on the World Health Organization (WHO) definition of sufficient iodine intake.[11,12] Hypothyroid women were excluded from the analysis. For women with urinary iodine levels less than 100 µg/L, the author found urinary perchlorate to be inversely associated with serum T4 levels and directly associated with TSH levels. For women with urinary iodine levels greater than or equal to 100 µg/L, the researchers found that perchlorate to be associated with increases in TSH but not a predictor of T4.

Steinmaus et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA], using the same data set, supported the findings of Blount et al. (2006) by demonstrating an interaction between thiocyanate/cotinine (byproducts of cigarette smoke), smoking, perchlorate, and impaired thyroid function in women with urinary iodine less than 100 µg/L. From the base population of women from

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[11] WHO notes that the prevalence of goiter begins to increase in populations with a median iodide intake level below 100 µg/L [ADDIN EN.CITE <EndNote><Cite><Author>WHO</Author><Year>1999</Year><RecNum>2119</RecNum><DisplayText>(Organization), 1999)</DisplayText><record><rec-number>2119</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541775351">2119</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>WHO (World Health Organization)</author></authors></contributors><titles><title>Progress toward the elimination of iodine deficiency disorders (IDD)</title></titles><dates><year>1999</year></dates><urls><related-urls><url>http://whqlibdoc.who.int/hq/1999/HWOO_NHD_99.4.pdf</url></related-urls></urls></record></Cite></EndNote>].

[12] Caldwell et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Caldwell</Author><Year>2005</Year><RecNum>2118</RecNum><DisplayText>(2005)</DisplayText><record><rec-number>2118</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1541775268">2118</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Caldwell, K.L.</author><author>R. Jones</author><author>J.G. Howell</author></authors></contributors><titles><title>Urinary iodine concentration: United States National Health and Nutrition Examination Survey 2001-2002</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>692-699</pages><volume>15</volume><number>7</number><dates><year>2005</year></dates><urls></urls></record></Cite></EndNote>] had found that about 36 percent of women living in the United States had iodine levels less than 100 µg/L in spot urine samples.

the NHANES (2001-2002). Steinmaus et al identified 385 women who had urinary iodine levels less than 100 µg/L and also had NHANES data on urinary perchlorate, creatinine, and thyroid hormone levels. Steinmaus et al. collected additional information for covariates that may impact the perchlorate-thyroid interaction such as race, age and hours fasted. Similar to Blount et al. (2006), Steinmaus et al. (2007) found an association between the log of urinary perchlorate in women with urinary iodide less than 100 µg/L and T4. The authors furthermore found when examining smokers (both as self-reported in NHANES or classified using cotinine levels), the association with T4 more than doubled in magnitude when compared to the entire study population. This same association was not seen with TSH. Additionally, when only looking at individuals with high thiocyanate exposure (> 1,800 µg/L), there was more than a doubling of the impact of perchlorate on urinary T4; again, this same affect was not seen for TSH.

Steinmaus et al. (2007) also observed a clear stepwise increase in the relationship between perchlorate and T4 with increasing levels of serum cotinine.[13] While clear associations between perchlorate, smoking, and decreased T4 were present in women with lower iodine intake levels, this relationship was not seen with TSH or with T4 in women with urinary iodide levels greater than or equal to 100 µg/L or in men. Additionally, the strongest perchlorate thyroid hormone associations were found with thiocyanate levels in the upper tertile (> 1,800 µg/L) and clear associations were not seen at levels less than 751 µg/L. These findings suggest that perchlorate may interact with tobacco smoke or thiocyanate to reduce iodide uptake by the thyroid and decrease thyroid function.

Building on the Blount et al. (2006) and Steinmaus et al. (2007) findings, Mendez and Eftim [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Mendez</Author><Year>2012</Year><RecNum>2244</RecNum><DisplayText>(2012)</DisplayText><record><rec-number>2244</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543350257">2244</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mendez, W.</author><author>Eftim, S.E.</author></authors></contributors><titles><title>Biomarkers of perchlorate exposure are correlated with circulating thyroid hormone levels in the 2007-2008 NHANES</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental Research</full-title></periodical><volume>118</volume><section>137-44</section><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>] evaluated NHANES data from the 2007-2008 survey cycle. Specifically, Mendez and Eftim (2012) used generalized additive mixed models to estimate the relationship between thyroid hormones concentrations in 1,887 subjects (970 male, 907 female) and creatinine corrected urinary perchlorate. In this analysis Mendez and Eftim (2012) controlled for phthalate esters and BPA based on previous research demonstrating the association of these biomarkers with thyroid hormones. Mendez and Eftim (2012) found perchlorate to be significantly associated with free and total T4 and free T3 in the entire cohort. When looking at males and females separately the authors found an inverse association between creatinine corrected urinary perchlorate and fT3, fT4 and total T4, though for females the associations were not statistically significant at the $p < 0.05$ level.

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[13] Cotinine is an alkaloid found in tobacco and is also a metabolite of nicotine. Cotinine may be a more accurate indicator of current smoking status than self-reported smoking.

Similarly, Steinmaus et al (2013) also utilized the 2007-2008 NHANES data to test the hypothesis that individuals with the highest perchlorate and thiocyanate exposure, along with low iodine intake, would have lower thyroid hormone levels than those with lower exposure and adequate iodine intake. To study this research question Steinmaus et al. (2013) created three groups from NHANES data: (1) a "low exposure" reference group that had urinary perchlorate and urinary thiocyanate concentration in the lowest tertile of concentrations and urinary iodine intake greater than 1,000 µg/L; (2) a "moderate exposure" group which included subjects who had a combination of urinary perchlorate and thiocyante in the middle tertile and urinary iodine greater than or equal to 100 µg/L; and (3) a "high exposure" group which has perchlorate and thiocyanate in the highest tertile and urinary iodine less than 100 µg/L. They then compared thyroid hormone concentrations in each group and determined the difference between them. They also evaluated the impact of each variable on thyroid hormone levels on their own. When comparing the highest tertile of perchlorate exposure participants to those with the lowest exposure there was a 5.0% difference in total T4. However, when comparing the "high exposure" group to the low exposure reference group the difference in total T4 was 12.9% indicating a substantial impact of the combined goitrogenic effect from the three variables assessed.

Suh, Abraham, Hixon & Proctor [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Suh</Author><Year>2014</Year><RecNum>2241</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>2241</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543349148">2241</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Suh, M.</author><author>Abraham, L.</author><author>Hixon, J.G.</author><author>Proctor, D.M.</author></authors></contributors><titles><title>The effects of perchlorate, nitrate, and thiocyanate on free thyroxine for potentially sensitive subpopulations of the 2001–2002 and 2007–2008 National Health and Nutrition Examination Surveys</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><pages>579-587</pages><volume>24</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>] also studied the associations between urinary perchlorate, nitrate and thiocyanate and serum fT4 in people with reduced urinary iodine levels using both 2001-2002 and 2007-2008 NHANES data (additional analysis was also done on pregnant women, which is summarized in the next section). Multivariate regression models, which included perchlorate, nitrate, thiocyanate and other covariates known to have an impact on the thyroid (e.g., TPO antibodies, race/ethnicity, BMI) were developed to test this association in both survey cycles. Additionally, a meta-analysis of the 2000-2001 data and the 2007-2008 data was also performed on the women only data. In non-pregnant women with creatinine-adjusted urinary iodine concentrations at or above 100 µg/L, perchlorate was found to be a significant predictor of serum fT4 in the 2001-2002 data cycle for one of the two presented models that included urinary perchlorate for this group. There was no statistically significant association between urinary perchlorate and serum fT4 for non-pregnant women with creatinine-adjusted urinary iodine concentrations below 100 µg/L.

McMullen, Ghassabian, Kohn & Trasande [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>McMullen</Author><Year>2017</Year><RecNum>2246</RecNum><DisplayText>(2017)</DisplayText><record><rec-number>2246</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

timestamp="1543354250">2246</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>McMullen, J.</author><author>Ghassabian, A.</author><author>Kohn, B.</author><author>Trasande, L.</author></authors></contributors><titles><title>Identifying subpopulations vulnerable to the thyroid-blocking effects of perchlorate and thiocyanate</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2637-2645</pages><volume>102</volume><number>7</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>] evaluated exposure to perchlorate, thiocyanate, and nitrate (measured in urine) and associated impacts on serum fT4 and TSH in 3,151 individuals using NHANES data from 2009 to 2012. Multivariate linear regression models were developed to test these associations as stratified by age and sex. The authors evaluated potential confounders likely associated with the thyroid hormone/goitrogen relationship controling for serum cotinine, body mass index, total daily energy consumption, race/ethnicity, and income-to-poverty ratio. Urinary iodide levels were not found to be correlated with any goitrogen and was therefore not included included as a covariate in the model. For each log unit increase in perchlorate, fT4 decreased with statistical significance by 0.026 ng/dL in the general population (4% decrease relative to median fT4, $p = 0.005$), 0.029 ng/dL in females (4% decrease relative to median fT4, $p = 0.035$), and by 0.055 ng/dL in adolescent females (aged 12-21, 8% decrease relative to median fT4, $p = 0.029$). There were no statistically significant associations between urinary perchlorate and serum fT4 for males alone or the other, older female age groups.

Overall studies of the general population have found an association between low levels of perchlorate exposure (measured in urine) and altered thyroid hormone status. The Mendez and Eftim (2012) and McMullen et al. (2017) analyses demonstrated this association across the entire cohort of adults. Studies by Blount et al. (2006) and Steinmaus (2007; 2013) point to the impact low iodine and exposures to other goitrogens may have on the perchlorate/thyroid hormone relationship.

7.2.3 Environmental Epidemiology Studies – Pregnant Women

In contrast to the general population studies which find fairly consistent associations between urinary perchlorate and changes in thyroid hormone, particularly in sensitive populations, studies specifically in pregnant women are more mixed. For example, Pearce et al. (2010, 2011 and 2012) did not find an association between perchlorate biomarkers and altered thyroid function in pregnant women. Pearce et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] conducted a cross-sectional study from 2002 to 2006 on approximately 1,000 women in Wales and Italy, who were less than 16 weeks pregnant at the time of enrollment. Urinary perchlorate levels were not found to be associated with serum TSH or fT4 in women with normal thyroid function or in the hypothyroid/hyperthyroxinemic women (Pearce et al., 2010). Additionally, when Pearce et al. (2010) excluded women with iodine levels less than 100 µg/L ($n = 604$), no association with TSH or fT4 was found. As noted by other researchers [ADDIN EN.CITE <EndNote><Cite><Author>California Environmental Protection Agency (CalEPA)</Author><Year>2015</Year><RecNum>62</RecNum><DisplayText>(California Environmental Protection Agency (CalEPA), 2015)</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437413166">62</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>California Environmental Protection Agency (CalEPA),</author></authors><secondary-authors><author>Office of Environmental Health

Hazard Assessment</author></secondary-authors></contributors><titles><title>Public health goal for perchlorate in drinking water</title></titles><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>] the median urine thiocyanate levels in Wales and Italy were much lower than those commonly found in the U.S., yet the reason for this is unknown given similar smoking prevalence in women in Wales, Italy, and the U.S. [ADDIN EN.CITE <EndNote><Cite><Author>World Health Organization</Author><Year>2008</Year><RecNum>488</RecNum><DisplayText>(United Kindom's Office of National Statistics, 2008; World Health Organization, 2008)</DisplayText><record><rec-number>488</rec-number><foreign-keys><key app="EN" db-id="zr9taef095wwxfe2zaqxw224vdvttr052wsx">488</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>World Health Organization,</author></authors></contributors><titles><title>Global Tobacco Epidemic 2008, Appendix III Table 3a</title></titles><dates><year>2008</year></dates><urls></urls></record></Cite><Cite><Author>United Kindom's Office of National Statistics</Author><Year>2008</Year><RecNum>489</RecNum><record><rec-number>489</rec-number><foreign-keys><key app="EN" db-id="zr9taef095wwxfe2zaqxw224vdvttr052wsx">489</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>United Kindom's Office of National Statistics,</author></authors></contributors><titles><title>General Lifestyle Survey: Smoking and Drinking among Adults, Table 1.10</title></titles><dates><year>2008</year></dates><urls></urls></record></Cite></EndNote>]. Regardless of why thiocyanate levels differ this may explain why associations were not found. In the Steinmaus et al. (2007) study conducted in the U.S., the strongest perchlorate thyroid hormone associations were found with thiocyanate levels in the upper tertile (> 1800 µg/L) and clear associations were not seen at levels less than 751 µg/L. The mean thiocyanate level was 407.5 µg/L in Wales and 372.5 µg/L in Italy. It has been argued that "the Pearce et al. (2010) findings [were] consistent with those of Steinmaus et al. (2007)" (CalEPA, 2015, p. 108).

Similarly, Pearce et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pearce</Author><Year>2011</Year><RecNum>450</RecNum><DisplayText>(2011)</DisplayText><record><rec-number>450</rec-number><foreign-keys><key app="EN" db-id="zr9taef095wwxfe2zaqxw224vdvttr052wsx">450</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pearce, E. N.</author><author>Spencer, C. A.</author><author>Mestman, J. H.</author><author>Lee, R. H.</author><author>Bergoglio, L. M.</author><author>Mereshian, P.</author><author>He, X.</author><author>Leung, A. M.</author><author>Braverman, L. E.</author></authors></contributors><auth-address>Section of Endocrinology, Diabetes and Nutrition, Boston University School of Medicine, Boston, MA.</auth-address><titles><title>The Effect of Environmental Perchlorate on Thyroid Function in Pregnant Women from Cordoba, Argentina, and Los Angeles, California</title><secondary-title>Endocr Pract</secondary-title></titles><periodical><full-title>Endocr Pract</full-title></periodical><pages>1-17</pages><dates><year>2011</year><pub-dates><date>Feb 16</date></pub-dates></dates><isbn>1934-2403 (Electronic)
1530-891X (Linking)</isbn><accession-num>21324827</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&do

pt=Citation&list_uids=21324827 </url></related-urls></urls><research-notes>Abt to Include</research-notes><language>Eng</language></record></Cite></EndNote>] found no association between urinary perchlorate concentrations and serum TSH, fT4 index, or total T3 values in pregnant women in Los Angeles, California, even though perchlorate was detected in the urine of all of the 134 women from California (median urinary perchlorate = 7.8 μg/L). The correlation between fT4 and urinary perchlorate was borderline significant, although it was in the opposite direction of what would have been expected from a biological standpoint ($r = 0.12$, $p = 0.06$). Their study population included women with low urinary iodine values (< 100 μg/L). The sample size in this study was much smaller ($n = 241$) which likely resulted in fewer participants with low iodide intake and less statistical power. Additionally, other goitrogenic anions in the blood and smoking status were not controlled in the study by Pearce et al. (2011). Pearce et al. (2011), however, did control for thyroperoxidase[14] antibodies in their analysis, which is an indicator of existing autoimmune thyroid disease, one of the factors that may affect the perchlorate-thyroid hormone relationship.

In a similar study based in Athens, Greece, Pearce et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pearce</Author><Year>2012</Year><RecNum>1396</RecNum><DisplayText>(2012)</DisplayText><record><rec-number>1396</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206441">1396</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pearce, E. N.</author><author>Alexiou, M.</author><author>Koukkou, E.</author><author>Braverman, L. E.</author><author>He, X.</author><author>Ilias, I.</author><author>Alevizaki, M.</author><author>Markou, K. B.</author></authors></contributors><titles><title>Perchlorate and thiocyanate exposure and thyroid function in first trimester pregnant women from Greece</title><secondary-title>Clinical Endocrinology</secondary-title><alt-title>Clin Endocrinol</alt-title><short-title>Clinical Endocrinology</short-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>471-474</pages><volume>77</volume><number>3</number><dates><year>2012</year></dates><isbn>ISSN 0300-0664
EISSN 1365-2265</isbn><label>1065842</label><urls><related-urls><url>http://dx.doi.org/10.1111/j.1365-2265.2012.04407.x</url></related-urls></urls><electronic-resource-num>10.1111/j.1365-2265.2012.04407.x</electronic-resource-num><language>English</language></record></Cite></EndNote>] evaluated the association between urinary perchlorate, iodine, and thiocyanate, and serum concentrations of TSH, fT4, fT3, and TPO antibodies in 134 pregnant women. The mean gestational age of the cohort was 10.9 weeks (SD ± 2.3 weeks) and mean concentrations were 135 μg/L (SD ± 77) for urinary iodine and 6.5 μg/L (SD ± 11.2) for perchlorate. In a Spearman's rank univariate correlation analysis, an inverse correlation was found between urinary perchlorate and serum fT4 in all women ($R = -0.19$; $p = 0.03$) and in the subgroup of 50 mildly iodine-deficient women with iodine levels below 100 μg/L ($R = -0.23$; $p = 0.09$). In multivariable regression modeling, with adjustments for urinary thiocyanate, urinary iodide, TPO antibody titers, gestational age, and maternal age, a relationship between the logarithm of urinary perchlorate (μg/L) and the logarithm of serum fT4 (pmol/L) was seen (regression coefficient

[14] Thyroperoxidase is an enzyme expressed mainly in the thyroid that frees iodine for addition onto Tg for the production of T4 or T3.

(β) = -0.007; p = 0.8) but it did not reach statistically significance. Gestational age was found to be inversely associated with fT4 in multivariable regression analyses (β = -0.003; p = 0.002 for the association between gestational age in days and the logarithm of serum fT4), and positively correlated with urinary perchlorate concentration (R = 0.18; p=0.04). Based on these results, the authors hypothesized that gestational age appeared to be a confounder in the apparent correlation between urine perchlorate and serum fT4 (and fT3; fT3 results are presented in the article). Associations between urinary perchlorate and TSH were not seen in correlation or regression analyses.

In Suh et al. (2014; methods summarized in the preceding section), pregnant women in the 2001-2002 survey cycle, did not have a significant association between urinary iodine less than 150 µg/L, nitrate, perchlorate or thiocyanate and fT4. However there were less than 50 pregnant women in the NHANES cohort and this group had the lowest urinary perchlorate out of any evaluated by the study authors. Further, NHANES does not define the gestational week of pregnancy and thyroid hormones vary significantly over the course of pregnancy which may explain some of this null finding.

Mortensen et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Mortensen</Author><Year>2016</Year><RecNum>2242</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>2242</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543349397">2242</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mortensen, M.E.</author><author>Birch, B.</author><author>Wong, L.</author><author>Valentin-Blasini, L. </author><author>Boyle, E.B.</author><author>Caldwell, K.L.</author><author>Merrill, L.S.</author><author>Moye, J.</author><author>Blount, B.C.</author></authors></contributors><titles><title>Thyroid antagonists and thyroid indicators in U.S. pregnant women in the Vanguard Study of the National Children's Study</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental Research</full-title></periodical><pages>179-188</pages><volume>149</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] also did not find an association between urinary perchlorate and thyroid hormone levels. In a study of 330 pregnant women from the Vanguard Study of the National Children's Study (women in this cohort are from seven locations: Queens County, New York; Duplin County, North Carolina; Salt Lake County, Utah; Orange County, California; Montgomery County, Pennsylvania; Waukesha County, Wisconsin) the authors evaluated urinary perchlorate, thiocyanate, nitrate iodine and serum fT4 and TSH and cotinine. Using multiple regression models the authors assessed of the potential inhibitors on thyroid hormone levels. They also assessed the impacts of perchlorate equivalent concentrations (which estimates the combined inhibitory effect of the anions on the NIS). They authors did not find an association between perchlorate or perchlorate equivalent concentrations and TSH or fT4, even in women with low iodine.

Contrary to the null findings from the Pearce, Suh and Mortensen studies, Charatcharoenwitthaya et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Charatcharoenwitthaya</Author><Year>2014</Year><RecNum>2243</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>2243</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543349625">2243</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Charatcharoenwitthaya, N.</author><author>Ongphiphadhanakul, B.</author><author>Pearce,

E.N.</author><author>Somprasit, C.</author><author>Chanthasenanont, A.</author><author>He, X.</author><author>Chailurkit, L.</author><author>Braverman, L.E.</author></authors></contributors><titles><title>The association between perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant Thai women</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2365-2371</pages><volume>99</volume><number>7</number><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>] found a direct association between urinary perchlorate and TSH and an inverse association between perchlorate and fT4. This study was conducted in 200 pregnant Thai women at 14 gestational weeks or less. In their multivariate analysis, adjusting for log thiocyanate to creatinine ratio, log iodide to creatinine ratio, and gestational age, log perchlorate to creatinine ratio was positively associated with log TSH and inversely associated with log free T4. Log thiocyanate to creatinine ratio was also a significant positive predictor of log TSH in women with a urine iodide level of less than 100 μg/L.

Horton et al., [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Horton</Author><Year>2015</Year><RecNum>2245</RecNum><DisplayText>(2015)</DisplayText><record><rec-number>2245</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1543350588">2245</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Horton, M.</author><author>Blount, B.</author><author>Valentin-Blasini, L.</author><author>Wapner, R.</author><author>Whyatt, R.</author><author>Gennings, C.</author><author>Factor-Litvak, P.</author></authors></contributors><titles><title>CO-occurring exposure to perchlorate, nitrate and thiocyanate alters thyroid function in healthy pregnant women</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental Research</full-title></periodical><pages>1-9</pages><volume>143</volume><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>] also found an association between perchlorate, when exposure co-occurs with nitrate and thiocyanate, and thyroid hormone status (as indicated by TSH) in a cohort from New York city. In this study the cross-sectional relationship between urinary perchlorate, thiocyanate and nitrate concentrations and thyroid function in 284 pregnant women at 12 (±2.8) weeks was evaluated. A weighted quantile sum (WQS) regression was used in the analysis. Serum fT4 and TSH were measured along with urine samples measuring perchlorate, nitrate and iodide. Results found urinary perchlorate, thiocyanate and nitrate concentrations were significantly correlated (Spearman's r 04.-0.5, $p<0.001$). Linear regression analysis did not suggest an association between the individual goitrogens and thyroid hormone functioning. However, the WQS exposed a significant positive relationship between the weighted sum of urinary concentrations of perchlorate, thiocyanate and nitrate and increased TSH, a significant relationship was not seen when looking at fT4. The WQS suggests that perchlorate was the main contributor to this relationship (weighted at 75%). These findings suggests that exposure to perchlorate, nitrate and thiocyanate may alter maternal thyroid function, specifically TSH, during pregnancy.

Additionally, Steinmaus et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Steinmaus</Author><Year>2016</Year><RecNum>258</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>258</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

timestamp="1468518705">258</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Steinmaus, C</author><author>Pearl, M</author><author>Kharrazi, M</author><author>Blount, BC</author><author>Miller, MD</author><author>Pearce, EN</author><author>Valentin-Blasini, L</author><author>DeLorenze G</author><author>Hoofnagle, AN</author><author>Liaw J</author></authors></contributors><titles><title>Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>861-867</pages><volume>124</volume><dates><year>2016</year></dates><urls></urls><electronic-resource-num><style face="underline" font="default" size="100%">http://dx.doi.org/10.1289/ehp.1409614</style></electronic-resource-num></record></Cite></EndNote>] found an association between perchlorate exposure (as measured by urinary perchlorate) and thyroid hormone levels (T4, fT4 and TSH) in pregnant women in San Diego. Data were collected as part of Project Baby's Breath during 2000-2003. During this time period the Colorado River, a large source of drinking water in the United States, was contaminated with perchlorate from a perchlorate manufacturing plant. Perchlorate concentrations during this time period in the river were 4 to 8 µg/L. Urine samples were collected from pregnant women at 7 gestational weeks (GW), and blood samples were collected from the same women around 15 to 20 GW. The median urinary perchlorate concentration in this population was 6.50 µg/L. According to Steinmaus et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Steinmaus</Author><Year>2016</Year><RecNum>258</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>258</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468518705">258</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Steinmaus, C</author><author>Pearl, M</author><author>Kharrazi, M</author><author>Blount, BC</author><author>Miller, MD</author><author>Pearce, EN</author><author>Valentin-Blasini, L</author><author>DeLorenze G</author><author>Hoofnagle, AN</author><author>Liaw J</author></authors></contributors><titles><title>Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>861-867</pages><volume>124</volume><dates><year>2016</year></dates><urls></urls><electronic-resource-num><style face="underline" font="default" size="100%">http://dx.doi.org/10.1289/ehp.1409614</style></electronic-resource-num></record></Cite></EndNote>], this is more than double the reported concentration of perchlorate in NHANES from 2001 to 2002.

Using multivariate regression analysis, Steinmaus et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Steinmaus</Author><Year>2016</Year><RecNum>258</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>258</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468518705">258</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Steinmaus, C</author><author>Pearl, M</author><author>Kharrazi, M</author><author>Blount, BC</author><author>Miller, MD</author><author>Pearce, EN</author><author>Valentin-Blasini,

L</author><author>DeLorenze G</author><author>Hoofnagle, AN</author><author>Liaw J</author></authors></contributors><titles><title>Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>861-867</pages><volume>124</volume><dates><year>2016</year></dates><urls></urls><electronic-resource-num><style face="underline" font="default" size="100%">http://dx.doi.org/10.1289/ehp.1409614</style></electronic-resource-num></record></Cite></EndNote>] evaluated the relationship between urinary perchlorate and thyroid hormone levels, specifically fT4, T4, and TSH. In their analysis perchlorate, thiocyanate, creatinine, and TSH were log_{10}-transformed to create normal distributions. Variables included in the final models due to *a priori* decision making included urinary creatinine concentrations, maternal age and education, ethnicity, and gestational age at serum collection. Additionally, the final models were adjusted for urinary thiocyanate, as it changed regression coefficients by more than 10%. Perchlorate-thyroid hormone analyses were also estimated after stratifying by urinary iodide categories of < 100, 100-300, and > 300 µg/day.

When evaluating all iodine groups, Steinmaus et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Steinmaus</Author><Year>2016</Year><RecNum>258</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>258</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468518705">258</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Steinmaus, C</author><author>Pearl, M</author><author>Kharrazi, M</author><author>Blount, BC</author><author>Miller, MD</author><author>Pearce, EN</author><author>Valentin-Blasini, L</author><author>DeLorenze G</author><author>Hoofnagle, AN</author><author>Liaw J</author></authors></contributors><titles><title>Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>861-867</pages><volume>124</volume><dates><year>2016</year></dates><urls></urls><electronic-resource-num><style face="underline" font="default" size="100%">http://dx.doi.org/10.1289/ehp.1409614</style></electronic-resource-num></record></Cite></EndNote>] found a statistically significant, inverse relationship between perchlorate and thyroid hormone (both fT4 and total T4). Further, there was a statistically significant, directly proportional relationship between perchlorate and log_{10}TSH. Evaluating these results as a whole, it can be seen that perchlorate exposures in the San Diego cohort are associated with depressed fT4, which may in turn result in an increase in TSH. However, this increase in TSH does not compensate for the decreased fT4 as a result of perchlorate exposure. This finding is supported by Fitzgerald and Bean [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Fitzgerald</Author><Year>2016</Year><RecNum>1876</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1876</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495213070">1876</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fitzgerald, S. P.</author><author>Bean, N. G.</author></authors></contributors><auth-address>Department of Internal Medicine and Department of Endocrinology, The Royal Adelaide Hospital, Adelaide, SA 5000, Australia; School of

Medicine, The University of Adelaide, Adelaide, SA 5005, Australia.
School of Mathematical Sciences, The University of Adelaide, Adelaide, SA 5005, Australia; ARC Centre of Excellence for Mathematical and Statistical Frontiers, The University of Adelaide, Adelaide, SA 5005, Australia.</auth-address><titles><title>The relationship between population T4/TSH set point data and T4/TSH physiology</title><secondary-title>Journal of Thyroid Research</secondary-title></titles><periodical><full-title>Journal of Thyroid Research</full-title></periodical><pages>6351473</pages><volume>2016</volume><edition>2016/04/29</edition><dates><year>2016</year></dates><isbn>2090-8067 (Print)</isbn><accession-num>27123359</accession-num><urls></urls><custom2>4830732</custom2><electronic-resource-num>10.1155/2016/6351473</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>], who evaluated thyroid hormone status in healthy and diseased populations and noted that although changes in T4 (as a result of levothyroxine dosing) have a predictable impact on TSH levels, increasing TSH levels do not have a consistently predictable impact on T4 levels [ADDIN EN.CITE <EndNote><Cite><Author>Fitzgerald</Author><Year>2016</Year><RecNum>1876</RecNum><DisplayText>(Fitzgerald & Bean, 2016)</DisplayText><record><rec-number>1876</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495213070">1876</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fitzgerald, S. P.</author><author>Bean, N. G.</author></authors></contributors><auth-address>Department of Internal Medicine and Department of Endocrinology, The Royal Adelaide Hospital, Adelaide, SA 5000, Australia; School of Medicine, The University of Adelaide, Adelaide, SA 5005, Australia.
School of Mathematical Sciences, The University of Adelaide, Adelaide, SA 5005, Australia; ARC Centre of Excellence for Mathematical and Statistical Frontiers, The University of Adelaide, Adelaide, SA 5005, Australia.</auth-address><titles><title>The relationship between population T4/TSH set point data and T4/TSH physiology</title><secondary-title>Journal of Thyroid Research</secondary-title></titles><periodical><full-title>Journal of Thyroid Research</full-title></periodical><pages>6351473</pages><volume>2016</volume><edition>2016/04/29</edition><dates><year>2016</year></dates><isbn>2090-8067 (Print)</isbn><accession-num>27123359</accession-num><urls></urls><custom2>4830732</custom2><electronic-resource-num>10.1155/2016/6351473</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>].

Steinmaus et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Steinmaus</Author><Year>2016</Year><RecNum>258</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>258</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468518705">258</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Steinmaus, C</author><author>Pearl, M</author><author>Kharrazi, M</author><author>Blount, BC</author><author>Miller, MD</author><author>Pearce, EN</author><author>Valentin-Blasini, L</author><author>DeLorenze G</author><author>Hoofnagle, AN</author><author>Liaw J</author></authors></contributors><titles><title>Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>861-867</pages><volume>124</volume><dates><year>2016</year></dates><urls></urls><electronic-

resource-num><style face="underline" font="default" size="100%">http://dx.doi.org/10.1289/ehp.1409614</style></electronic-resource-num></record></Cite></EndNote>] found the effect of perchlorate on fT4 levels to be similar among women with low (<100 µg/day) and normal (100-300 µg/day) iodine intakes. They found a greater effect of perchlorate on fT4 in the high-iodine intake group (>300 µg/day). Their hypothesis for this finding is as follows:

> *In most individuals, very high iodine intakes transiently and paradoxically inhibit thyroid hormone production, termed the acute Wolff–Chaikoff effect [ADDIN EN.CITE <EndNote><Cite><Author>Wolff</Author><Year>1948</Year><RecNum>1826</RecNum><DisplayText>(Wolff & Chaikoff, 1948)</DisplayText><record><rec-number>1826</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206448">1826</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Wolff, J.</author><author>Chaikoff, I. L.</author></authors></contributors><titles><title>Plasma inorganic iodide as a homeostatic regulator of thyroid function</title><secondary-title>Journal of Biological Chemistry</secondary-title><alt-title>J Biol Chem</alt-title><short-title>Journal of Biological Chemistry</short-title></titles><periodical><full-title>Journal of Biological Chemistry</full-title><abbr-1>J Biol Chem</abbr-1></periodical><alt-periodical><full-title>Journal of Biological Chemistry</full-title><abbr-1>J Biol Chem</abbr-1></alt-periodical><pages>555-564</pages><volume>174</volume><number>2</number><dates><year>1948</year></dates><isbn>ISSN 0021-9258
EISSN 1083-351X</isbn><label>2140877</label><urls></urls><language>English</language></record></Cite></EndNote>]. Normally, this is only temporary, and after a short disruption there is an "escape" and thyroid function returns to normal after a few days, even if high iodine exposure continues [ADDIN EN.CITE <EndNote><Cite><Author>Eng</Author><Year>1999</Year><RecNum>1902</RecNum><DisplayText>(Eng et al., 1999)</DisplayText><record><rec-number>1902</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1500664291">1902</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Eng, P.H.</author><author>Cardona, G.R.</author><author>Fang, S.L.</author><author>Previti, M.</author><author>Alex, S.</author><author>Carrasco, N.</author></authors></contributors><titles><title>Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein</title><secondary-title>Endocrine Journal</secondary-title></titles><periodical><full-title>Endocrine Journal</full-title></periodical><pages>3404-3410</pages><volume>140</volume><dates><year>1999</year></dates><*

urls></urls></record></Cite></EndNote>]. However, several studies have reported increased rates of thyroid autoimmunity and hypothyroidism in areas where people have chronically high iodine intakes, from diet (e.g., seaweed consumption) or drinking water with naturally high iodine concentrations. This would suggest that chronic excessive high iodine intakes can lead to long-term hypothyroidism in susceptible individuals [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Associations between very high urinary iodide concentrations and decreased thyroid hormone production have also been seen in NHANES [ADDIN EN.CITE <EndNote><Cite><Author>Cushing</Author><Year>2011</Year><RecNum>1908</RecNum><DisplayText>(Cushing, Steinmaus, Miller, & Smith, 2011; Vanderver, Engel, & Lamm, 2007)</DisplayText><record><rec-number>1908</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1500666487">1908</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Cushing, L.</author><author>Steinmaus, C.</author><author>Miller, M.D.</author><author>Smith, A.H.</author></authors></contributors><titles><title>The effects of high iodine intake on perchloraterelated decreases in thyroid hormone, NHANES 2001–2 [Abstract 0-0128]. In: Abstracts of the 2011 Conference of the International Society for Environmental Epidemiology (ISEE)</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><dates><year>2011</year></dates><urls></urls></record></Cite><Cite><Author>Vanderver</Author><Year>2007</Year><RecNum>1907</RecNum><record><rec-number>1907</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1500666355">1907</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Vanderver, G.B.</author><author>Engel, A.</author><author>Lamm, S.</author></authors></contributors><titles><title>Cigarette smoking and iodine as hypothyroxinemic stressors in U.S. women of childbearing age: a NHANES III analysis</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><volume>17</volume><section>741-746</section><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>]. Overall, these studies, combined with our findings, suggest that excessive iodine intakes could lead to altered thyroid function and an enhanced susceptibility to perchlorate. (p. 865)

Steinmaus et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Steinmaus</Author><Year>2016</Year><RecNum>258</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>258</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

timestamp="1468518705">258</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Steinmaus, C</author><author>Pearl, M</author><author>Kharrazi, M</author><author>Blount, BC</author><author>Miller, MD</author><author>Pearce, EN</author><author>Valentin-Blasini, L</author><author>DeLorenze G</author><author>Hoofnagle, AN</author><author>Liaw J</author></authors></contributors><titles><title>Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>861-867</pages><volume>124</volume><dates><year>2016</year></dates><urls></urls><electronic-resource-num><style face="underline" font="default" size="100%">http://dx.doi.org/10.1289/ehp.1409614</style></electronic-resource-num></record></Cite></EndNote>] also noted a correlation between perchlorate and iodine. It is difficult to hypothesize why exposure to perchlorate would be correlated with increased iodine levels. However, given this correlation, if individuals with higher perchlorate exposure also had higher iodine intake, there may have been uncontrolled confounding that could have diminished the beta estimate.

Additionally, Knight et al. (2018) evaluated 308 third trimester pregnant women at 36-38 weeks gestation and found urinary perchlorate to be inversely related to fT4. Specifically, in a cohort of women from South-West England, urinary iodine, perchlorate and thiocyante was measured along with fT4, TSH and TPO-Ab. Using multiregression analysis the authors found that for every 10 percent increase in urinary perchlorate there was a 0.03 pmol/L decrease in maternal serum fT4.

Overall, the studies specifically evaluating pregnant women's exposure to perchlorate and its potential association with thyroid hormone levels is mixed with the Pearce et al. (2010, 2011, 2012), Suh et al. (2014) and Mortensen et al. (2016) not finding an association while Steinmaus et al. (2016) and Charatcharoenwitthaya et al. (2014) see an association. Further, Knight et al. (2018) also saw an association when perchlorate co-occurs with other goitrogens. These possible explanations for the differences in findings include that the study populations are from different countries and different populations of women who may have different co-exposures, different iodine intake status and variable gestational age, which has a profound impact on circulating thyroid hormone levels.

7.2.4 Environmental Epidemiology Studies – Infants

Cao et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Cao</Author><Year>2010</Year><RecNum>125</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>125</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466187678">125</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Cao, Y.</author><author>Blount, B. C.</author><author>Valentin-Blasini, L.</author><author>Bernbaum, J. C.</author><author>Phillips, T. M.</author><author>Rogan, W. J.</author></authors></contributors><auth-address>Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA.</auth-address><titles><title>Goitrogenic anions, thyroid-stimulating hormone, and thyroid hormone in infants</title><secondary-title>Environ Health Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-

title></periodical><pages>1332-
7</pages><volume>118</volume><number>9</number><edition>2010/05/05</edition><keywords
><keyword>Antithyroid Agents/urine</keyword><keyword>Environmental Exposure/adverse
effects</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Infant</
keyword><keyword>Infant,
Newborn</keyword><keyword>Iodides/urine</keyword><keyword>Male</keyword><keyword>Ni
trates/toxicity/urine</keyword><keyword>Perchlorates/toxicity/urine</keyword><keyword>Thiocya
nates/toxicity/urine</keyword><keyword>Thyroid Hormones/
urine</keyword><keyword>Thyrotropin/
toxicity</keyword></keywords><dates><year>2010</year><pub-dates><date>Sep</date></pub-
dates></dates><isbn>1552-9924 (Electronic)
0091-6765 (Linking)</isbn><accession-
num>20439182</accession-num><urls></urls><custom2>2944098</custom2><electronic-resource-
num>10.1289/ehp.0901736</electronic-resource-num><remote-database-provider>NLM</remote-
database-provider><language>eng</language></record></Cite></EndNote>] examined the association of urinary perchlorate, nitrate, iodide, and thiocyanate with urinary T4 and TSH in infants and examined if these associations differed by sex or iodide status, using data and samples from the Study of Estrogen Activity and Development. (Note: the other studies described evaluated serum, not urinary, T4 and TSH.) Cao et al.'s study included 92 full-term infants between birth and 1 year of age. Perchlorate thiocyanate, nitrate, and iodide were measured in 206 urine samples; TSH and T4 were measured in 50 blood and 206 urine samples. Using mixed models, Cao et al. determined infants with higher urinary perchlorate, nitrate, or thiocyanate had higher urinary TSH. When all three covariates were modeled together, children with higher nitrate and thiocyanate had higher urinary TSH, but higher perchlorate was associated with TSH only in children with low iodide. The interpretation of this study is made more difficult by the contradictory finding that with more perchlorate, the infants' urinary T4 levels tended to be higher; this was the opposite of what is expected. Further, how urinary TSH (or T4) relates to serum thyroid hormone levels is a question that complicates the interpretation of these study results.

Using a cohort of 64 mother infant pairs from Boston, Massachusetts Leung et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] studied the potential association between infant (1-3 months old) exposures to perchlorate, thiocyanate and iodine (measured in maternal breast milk and also infant urine) and thyroid function. Maternal urinary perchlorate was also measured. Median (range) perchlorate concentrations were 4.4 µg/L (0.5-29.5 µg/L) in breast milk, 3.1 µg/L (0.2-22.4 µg/L) in maternal urine, and 4.7 µg/L (0.3-25.3 µg/L) in infant urine. Urine iodine concentrations were 101.9 µg/L (27-570 µg/L) in mothers and 197.5 µg/L (40-785 µg/L) in infants. In multivariable regression analyses which included breast milk, maternal urine, and infant urine thiocyanate concentrations, no evidence of an association was seen between breast milk, maternal urine, and infant urine perchlorate concentration and infant serum fT4 (logarithm transformed) or TSH (logarithm transformed). The authors noted that they were not able to achieve their targeted enrollment of 275 mother-infant pairs, and state that, "The recruited study population was underpowered to determine the statistical significance of perchlorate and thiocyanate exposures on serum infant thyroid function."

A study by Ucal et al. [ADDIN EN.CITE <EndNote><Cite
ExcludeAuth="1"><Author>Ucal</Author><Year>2018</Year><RecNum>2240</RecNum><Displ
ayText>(2018)</DisplayText><record><rec-number>2240</rec-number><foreign-keys><key
app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"
timestamp="1543347914">2240</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Ucal, Y.</author><author>Sahin, O.N.</author><author>Serdar, M.</author><author>Blount, B.</author><author>Kumru, P.</author><author>Muhcu, M.</author><author>Eroglu, M.</author><author>Akin-Levi, C.</author><author>Keles, Z.</author><author>Turam, C.</author><author>Valentin-Blasini, L.</author><author>Morel-Espinosa, M.</author><author>Serteser, M.</author><author>Unsal, I.</author><author>Ozpinar, A.</author></authors></contributors><titles><title>Exposure to perchlorate in lactating women and its associations with newborn thyroid stimulating hormone</title><secondary-title>Frontiers in Endocrinology</secondary-title></titles><periodical><full-title>Frontiers in endocrinology</full-title></periodical><volume>9</volume><section>348</section><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>] studied 185 mother child pairs from Istanbul, Turkey and the association between maternal urinary perchlorate, thiocyanate and nitrate concentrations and thyroid hormone concentrations in infants. Thyroid hormones were measured in both the mothers (blood collected with 48 hours of delivery) and the infants (blood collected between 48 and 72 hour after delivery). Perchlorate was also analyzed in the colostrum. The medians of maternal urinary perchlorate (4.00μg/g creatinine), maternal urinary thiocyanate (403μg/g creatinine), and maternal urinary nitrate (49,117μg/g creatinine) were determined. Having concentrations of all three urinary NIS inhibitors (μg/g creatinine) above their 75th percentile levels was significantly correlated with higher newborn TSH($r = 0.21$, $p < 0.001$), however having two or one of the NIS inhibitor concentrations above the 75th percentile had no statistically significant association with newborn TSH. Median colostrum perchlorate level concentration of all 185 participants was 2.30 μg/L. Colostrum perchlorate was not significantly correlated with newborn TSH ($p > 0.05$); however, there was a significant correlation between colostrum perchlorate level and maternal TSH ($r = 0.21$, $p < 0.01$). Similarly, there was a significant positive association between colostrum perchlorate and maternal urinary creatinine adjusted perchlorate ($r = 0.32$, $p < 0.001$).

The limited evidence on perchlorate exposures in infants (measured as a proxy through breast milk or maternal or infant urine) demonstrated mixed results on the association between perchlorate and thyroid function. The power in the cited studies to detect an effect is small, with the greatest n equal to 185.

7.3 Summary

In summary, most low dose clinical studies have not seen an association between perchlorate dosing and thyroid hormone levels, but in most instances have observed reduced iodine uptake by the thyroid gland. On the contrary, many U.S. based general population studies have observed an association between low level perchlorate exposure and changes in thyroid hormone levels, with the impact being greatest in individuals with low iodine or co-exposures to other goitrogens. Additionally, the evidence for potentially sensitive populations of pregnant women is more mixed. The evidence in infants is also much more limited.

Exposures to perchlorate and resulting changes in thyroid hormone levels may lead to adverse health effects, particularly in sensitive populations such as pregnant women, fetuses, and infants (Taylor et al., 2014). Thyroid hormones are critical to neurodevelopment of the fetus, and requirements for these hormones increase during pregnancy [ADDIN EN.CITE <EndNote><Cite><Author>Leung</Author><Year>2010</Year><RecNum>117</RecNum><DisplayText>(Leung, Pearce, & Braverman, 2010)</DisplayText><record><rec-number>117</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

timestamp="1465915921">117</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leung, A. M.</author><author>Pearce, E N</author><author>Braverman, L</author></authors></contributors><titles><title>Perchlorate, iodine and the thyroid</title><secondary-title>Best Practice & Research Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>Best Practice & Research Clinical Endocrinology & Metabolism</full-title></periodical><pages>133-141</pages><volume>24</volume><number>1</number><dates><year>2010</year></dates><isbn >1521-690X</isbn><urls></urls></record></Cite></EndNote>]. Taylor et al. (2014) found that mothers in the upper 10th percentile of perchlorate exposure during pregnancy had significantly increased odds of having offspring with intelligence quotient (IQ) scores in the lowest 10% of the population. The next section describes the assessment of potentially sensitive populations to potential perturbations in thyroid hormone homeostasis caused by perchlorate exposure.

8. Potentially Sensitive Life Stages

Because SDWA requires that the MCLG be set at the level at which there are no adverse effects to the health of persons and because SDWA requires that EPA assess the effects of the contaminant on subpopulations likely to be at greater risk from exposure to the contaminant, EPA identifies the most sensitive populations to derive the MCLG. The SAB states, "the sensitive populations that EPA should consider for exposure to perchlorate are the fetuses of hypothyroxinemic pregnant women, and infants exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women" [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Suffix>` ; p. 11</Suffix><DisplayText>(SAB, 2013; p. 11)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>]. The current analysis presented in this document aims to protect the fetus of a hypothyroxinemic pregnant woman. More specifically, the ultimate MCLG is based on protecting the fetus of a first trimester pregnant mother with low-iodine intake levels (i.e., 75 µg/kg/day), low fT4 levels (i.e., 10th percentile of a fT4 distribution for individuals with 75 µg/day iodine intake), and weak TSH feedback strength (defined as TSH feedback reduced to approximately 60 percent less effective than for the median individual). This section evaluates if protecting this population will also be protective of breast- and bottle-fed infants by evaluating two sensitivities: (1) the sensitivity of the thyroid to perchlorate exposure for each population, and (2) the sensitivity of the brain to thyroid hormone perturbations.

8.1 Sensitivity of the Thyroid to Perchlorate Exposure

To directly compare the relative sensitivities of the predicted impacts of perchlorate exposure on thyroid hormones, EPA can evaluate the BBDR model predictions for changes in fT4 for the breast- and formula-fed infant and compare these changes to the predictions for the first trimester pregnant mother.[15] Given that the fetus does not yet have an operational thyroid in the first trimester, it is fully dependent on the mother's thyroid [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><DisplayText>(Zoeller & Rovet, 2004)</DisplayText><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet,

[15] The breast- and formula-fed infant BBDR model was peer reviewed in January 2017. No updates were made to the models for these life stages as a result of the peer review, given the strong recommendation from the review panel to develop a first trimester model. However, to directly compare the changes in fT4 for specific doses of perchlorate, the 2017 peer-reviewed model must be used. (For more information on these breast- and bottle-fed infant models, see the *Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water* (March 29, 2017).)

J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>]. Subsequently, the thyroid hormone levels predicted for the first trimester pregnant mother represent the hormone levels available to the fetus.

Although formula-fed infants are potentially vulnerable to increased impacts of contaminants in drinking water given their high intake rates per unit of bodyweight, the BBDR model demonstrated that perchlorate barely impacts the thyroid hormone levels for 30-, 60-, and 90-day formula-fed infants, even up to doses as high as 20 µg/kg/day. Specifically, "the range of iodine levels in formula is sufficient to almost entirely offset the effects of perchlorate exposure at 30, 60 and 90 days" [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2016</Year><RecNum>246</RecNum><Suffix>`; p. 73</Suffix><DisplayText>(U.S. EPA, 2016; p. 73)</DisplayText><record><rec-number>246</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468339271">246</key></foreign-keys><ref-type name="Generic">13</ref-type><contributors><authors><author>U.S. EPA,</author></authors><secondary-authors><author>Paul Schlosser, Teresa Leavens, and Santhini Ramasamy</author></secondary-authors></contributors><titles><title>Biologically based dose response models for the effect of perchlorate on thyroid hormones in the infant, breast feeding mother, pregnant mother, and fetus: model development, revision, and preliminary dose-response analyses </title><secondary-title>Peer Review Draft</secondary-title></titles><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].[16] The day-7 infant showed a slightly steeper dose-response curve than the very shallow dose-responses of the 30, 60 and 90 day infants. For the day-7 infant, it was assumed that perchlorate exposure occurred as a fetus through day 7 and that the mother had an iodine intake rate of 200 µg/day. It is therefore concluded that the steeper dose-response for the day-7 infant was a result of "in utero exposure with

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[16] The ranges of iodine intake are based on data presented in [HYPERLINK \l "_ENREF_108" \o "Pearce, 2004 #1400"]. Note that two samples in [HYPERLINK \l "_ENREF_108" \o "Pearce, 2004 #1400"] were soy-based formulas. Soy-based formulas have isoflavones, which disrupt the normal thyroid function, although there is debate about the impact of isoflavones from soy formulas [ADDIN EN.CITE <EndNote><Cite><Author>Canadian Paediatric Society</Author><Year>2009</Year><RecNum>2021</RecNum><DisplayText>(Canadian Paediatric Society, 2009)</DisplayText><record><rec-number>2021</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1532367237">2021</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Canadian Paediatric Society,</author></authors></contributors><titles><title>Concerns for the use of soy-based formulas in infant nutrition</title><secondary-title>Paediatrics & Child Health </secondary-title></titles><periodical><full-title>Paediatrics & Child Health</full-title></periodical><pages>109-113</pages><volume>14</volume><number>2</number><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. The BBDR model did not consider other ingredients in the formula that may impact the perchlorate/thyroid hormone relationship.

border-line inadequate maternal iodine ingestion" [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2016</Year><RecNum>246</RecNum><Suffix>`; p. 73</Suffix><DisplayText>(U.S. EPA, 2016; p. 73)</DisplayText><record><rec-number>246</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468339271">246</key></foreign-keys><ref-type name="Generic">13</ref-type><contributors><authors><author>U.S. EPA,</author></authors><secondary-authors><author>Paul Schlosser, Teresa Leavens, and Santhini Ramasamy</author></secondary-authors></contributors><titles><title>Biologically based dose response models for the effect of perchlorate on thyroid hormones in the infant, breast feeding mother, pregnant mother, and fetus: model development, revision, and preliminary dose-response analyses </title><secondary-title>Peer Review Draft</secondary-title></titles><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. By day 30, it is clear the iodine in the formula has offset the inadequate maternal iodine intake and the fetal perchlorate. The EPA has concluded that based on the BBDR model results for the formula-fed infant, any value set for the MCLG based on the fetus of the first trimester hypothyroxinemic pregnant mother would also protect the formula-fed infant.

To determine if the same would be true for the breast-fed infant, the EPA compared the predicted percent change in fT4 experienced for given doses of perchlorate for both the breast-fed infant and the fetus of a first trimester, low-iodine intake (75 µg/day) pregnant mother. This comparison is presented in [REF _Ref519676368 \h]. Given that the current version of the BBDR model contains a TSH feedback loop and the infant models previously developed did not contain this loop, this comparison is done with the feedback loop turned off.[17]

[REF _Ref519676368 \h * MERGEFORMAT] shows that when exposed to the same doses of perchlorate at iodine intakes of 75 and 100 µg/day, the first trimester pregnant mother has the largest resulting percent change in fT4 when compared to the 30- and 60-day infant. However, in the 50 µg/day iodine intake group, the 30-day infant is the most sensitive to changes in perchlorate, while approximately the same percent reduction in fT4 is seen when comparing the 60-day infant to the first trimester mother. In order to understand the relative sensitivity of the first trimester fetus compared to the breast-fed infant, it is necessary to understand the neurodevelopmental implications of the fT4 changes seen in [REF _Ref519676368 \h], as similar perturbations in thyroid hormones could have different neurodevelopmental effects based on life-stage. The relative sensitivity of the brain to perturbations in thyroid hormones between the first trimester fetus and the breast-fed infant is considered in the subsequent section.

[17] Ideally this comparison would be done with a TSH feedback loop in the infant models as well. However, given the need to move forward with the analysis in the given time frame this was not feasible.

Table [SEQ Table * ARABIC]. Predicted Changes in fT4 for Given Maternal Iodine Intakes and Perchlorate Doses for the Pregnant Mother, 30-Day and 60-Day Breast-Fed Infant

Maternal Iodine Intake (µg/d)	Maternal Perchlorate Dose (µg/kg/day)	Predicted fT4 Concentration (pmol/L) (% change from 0 dose of perchlorate)		
		1st Trimester	Breast-Fed Infant	
		GW12[a]	30 days	60 days
100	0	10.32	25.31	25.23
	2	10.13 (-1.84%)	25.07 (-0.95%)	25.00 (-0.91%)
	4	9.91 (-3.97%)	24.82 (-1.94%)	24.75 (-1.90%)
75	0	8.18	24.86	24.76
	2	7.92 (-3.18%)	24.47 (-1.65%)	24.42 (-1.37%)
	4	7.67 (-6.23%)	24.04 (-3.30%)	24.05 (-2.87%)
50	0	5.50	23.02	23.54
	2	5.32 (-3.27%)	21.84 (-5.13%)	22.83 (-3.02%)
	4	5.14 (-6.55%)	20.64 (-10.34%)	22.03 (-6.41%)

[a] The TSH feedback loop is turned off for these analyses in order to compare the infant model that did not have a TSH feedback loop component.

8.2 Sensitivity of the Brain to Perturbations in Thyroid Hormones

The literature clearly indicates that minor perturbations in thyroid hormone levels in the first trimester mother can adversely impact the offspring's neurodevelopment. As stated by the SAB (and supported by the literature review in the Approaches Report), "Children exposed gestationally to maternal hypothyroxinemia (without hypothyroidism) show reduced levels of global and specific cognitive abilities, as well as increased rates of behavior problems including greater dysregulation in early infancy and attentional disorders in childhood [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Notably these effects are correlated with both degree [ADDIN EN.CITE ADDIN EN.CITE.DATA] and duration [ADDIN EN.CITE <EndNote><Cite><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(Pop et al., 2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><url

s></urls></record></Cite></EndNote>] of maternal hypothyroxinemia" [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Suffix>` ; p. 10</Suffix><DisplayText>(SAB, 2013; p. 10)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>].

The literature does not provide analogous evidence linking minor perturbations in thyroid hormones in infants to adverse neurodevelopmental outcomes. As stated by the California Environmental Protection Agency (CalEPA) in their assessment of a public health goal for perchlorate, "the fetus is highly sensitive to any changes in thyroid hormone levels during pregnancy. It is unknown whether the neonate is similarly sensitive" [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>California Environmental Protection Agency (CalEPA)</Author><Year>2015</Year><RecNum>62</RecNum><Prefix>CalEPA`, </Prefix><Suffix>`; p. 90</Suffix><DisplayText>(CalEPA, 2015; p. 90)</DisplayText><record><rec-number>62</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437413166">62</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>California Environmental Protection Agency (CalEPA),</author></authors><secondary-authors><author>Office of Environmental Health Hazard Assessment</author></secondary-authors></contributors><titles><title>Public health goal for perchlorate in drinking water</title></titles><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>]. One study was located that evaluated both the impact of maternal hypothyroxinemia and infant fT4 levels on subsequent neurodevelopmental outcomes. [HYPERLINK \l "_ENREF_33" \o "Costeira, 2011 #7"] found that children born to mothers with low fT4 in the first trimester had increased odds of mild-to-severe delays in psychomotor development compared to children born to mothers with normal fT4 levels but that neonatal thyroid status (measured on day 3 after birth) did not influence development. [HYPERLINK \l "_ENREF_58" \o "Henrichs, 2010 #928"] found in their evaluation that the neonatal thyroid status (measured in cord blood) did not explain the relationship between maternal hypothyroxinemia, early pregnancy, and children's cognitive impairment.

However, the SAB pointed out two lines of evidence that suggested that "the infant may be vulnerable to perchlorate exposure" preterm infants that experience transient hypothyroxinemia of prematurity (THOP) and infants that experience congenital hypothyroidism (SAB, 2013, p. 11). According to the SAB, "THOP arises because the fetal thyroid system is immature if a child is born preterm and the late-gestational maternal iodine and thyroid hormone supplies are no longer available [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Follow-up studies of THOP report reduced [intelligence quotient] (IQ) [ADDIN EN.CITE <EndNote><Cite><Author>Lucas</Author><Year>1996</Year><RecNum>2015</RecNum><DisplayText>(Lucas, Morley, & Fewtrell, 1996)</DisplayText><record><rec-number>2015</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1532362612">2015</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>A. Lucas</author><author>R. Morley </author><author>M. Fewtrell</author></authors></contributors><titles><title>Low triiodothyronine concentration in preterm infants and subsequent intelligence quotient at 8-year follow up</title><secondary-title>Brit Med J</secondary-title></titles><periodical><full-title>Brit Med J</full-title></periodical><pages>1132-3</pages><volume>312</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>], impaired visual skills [ADDIN EN.CITE <EndNote><Cite><Author>Rovet</Author><Year>2008</Year><RecNum>2016</RecNum><DisplayText>(Rovet & Simic, 2008)</DisplayText><record><rec-number>2016</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1532362698">2016</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rovet, J</author><author>N. Simic</author></authors></contributors><titles><title>The role of transient hypothyroxinemia of prematurity in development of visual abilities</title><secondary-title>Sem Perinatol</secondary-title></titles><periodical><full-title>Sem Perinatol</full-title></periodical><pages>431-7</pages><volume>32</volume><dates><year>2008</year></dates><urls></urls></record></Cite></EndNote>] and an increased incidence of neurological dysfunction and school failure [ADDIN EN.CITE <EndNote><Cite><Author>Ouden</Author><Year>1996</Year><RecNum>2017</RecNum><DisplayText>(Ouden, Kok, Verkerk, Brand, & Verloove-Vanhorick, 1996)</DisplayText><record><rec-number>2017</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1532362793">2017</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>A.L. Den Ouden</author><author>J.H. Kok</author><author>P.H. Verkerk</author><author>R. Brand</author><author>S.P. Verloove-Vanhorick</author></authors></contributors><titles><title>The relation between neonatal thyroxine levels and neurodevelopmental outcome at Age 5 and 9 years in a national cohort of very preterm and/or very low birth weight infants</title><secondary-title>Pediatr Res</secondary-title></titles><periodical><full-title>Pediatr Res</full-title></periodical><pages>142-5</pages><volume>39</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>], cognitive disabilities [ADDIN EN.CITE <EndNote><Cite><Author>Simic</Author><Year>2010</Year><RecNum>2014</RecNum><DisplayText>(Simic & Rovet, 2010)</DisplayText><record><rec-number>2014</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1532362522">2014</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>N. Simic</author><author>J. Rovet</author></authors></contributors><titles><title>Transient hypothyroxinemia of prematurity: current state of knowledge</title><secondary-title>Thyroid Intern</secondary-title></titles><periodical><full-title>Thyroid Intern</full-title></periodical><pages>1-13</pages><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>], cerebral palsy [ADDIN EN.CITE <EndNote><Cite><Author>Reuss</Author><Year>1996</Year><RecNum>2018</RecNum><DisplayText>(Reuss, Paneth, Pinto-Martin, Lorena, & Susser, 1996)</DisplayText><record><rec-number>2018</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1532363214">2018</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>M. L.

Reuss</author><author>N. Paneth</author><author>J. A. Pinto-Martin</author><author>J. M. Lorena</author><author>M. Susser</author></authors></contributors><titles><title>The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age</title><secondary-title>New Engl J Med</secondary-title></titles><periodical><full-title>New Engl J Med</full-title></periodical><pages>821-7</pages><volume>334</volume><dates><year>1996</year></dates><urls></urls></record></Cite></EndNote>] with the most severe effects being seen in the lowest levels of thyroid hormones. Further, congenital hypothyroidism, which arises from a defect in thyroid gland formation or function or its central regulation by the hypothalamus and pituitary [ADDIN EN.CITE <EndNote><Cite><Author>Rovet</Author><Year>2003</Year><RecNum>2019</RecNum><DisplayText>(Rovet & Daneman, 2003)</DisplayText><record><rec-number>2019</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1532363287">2019</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rovet, J</author><author>D. Daneman</author></authors></contributors><titles><title>Congenital hypothyroidism: a review of current diagnostic procedures and treatment</title><secondary-title>Pediatric Drugs</secondary-title></titles><periodical><full-title>Pediatric Drugs</full-title></periodical><pages>141-149</pages><volume>5</volume><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>], is associated with mental retardation and severe behavior problems if untreated in the newborn period [ADDIN EN.CITE <EndNote><Cite><Author>Rovet</Author><Year>1992</Year><RecNum>2020</RecNum><DisplayText>(Rovet, Ehrlich, & Sorbara, 1992)</DisplayText><record><rec-number>2020</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1532363431">2020</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rovet, J</author><author>R. M. Ehrlich</author><author>D. L. Sorbara</author></authors></contributors><titles><title>Neurodevelopment in infants and preschool children with congenital hypothyroidism: etiological and treatment factors affecting outcome</title><secondary-title>Journal of Pediatric Psychology</secondary-title></titles><periodical><full-title>Journal of Pediatric Psychology</full-title></periodical><pages>187-213</pages><volume>17</volume><number>2</number><dates><year>1992</year></dates><urls></urls></record></Cite></EndNote>]" [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Suffix>` ; p. 11</Suffix><DisplayText>(SAB, 2013; p. 11)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>].

Clearly sufficient thyroid hormone levels in infancy are necessary for the infant brain to develop properly. However, the evidence linking perturbations in thyroid hormone levels to disrupted neurodevelopment for infants is in individuals with clinical conditions (i.e., THOP and congenital hypothyroidism). It is unknown if minor perturbations in thyroid hormones in infants would result in

adverse neurodevelopmental outcomes similar to that seen in the literature for the offspring of first trimester pregnant mothers with hypothyroxinemia. Therefore, maternal thyroid hormone perturbations in the first trimester may be more significantly associated with the offspring neurodevelopment [ADDIN EN.CITE ADDIN EN.CITE.DATA] than infant thyroid hormones. The EPA concludes that deriving and MCLG to protect a fetus in the first trimester will be protective of other potentially sensitive life stages as well.

9. Select the Approach to Inform the POD

Consistent with SAB recommendations, the EPA connected modeled thyroid hormone effects from perchlorate exposure in pregnant women to neurodevelopmental outcomes in their offspring. This was done using a combination of the BBDR model and the epidemiology literature that relates changes in maternal thyroid hormones to neurodevelopmental outcomes in children. This process is described in [REF _Ref516151159 \h].

For each step of this process, decisions were made about the most appropriate inputs to the analysis. In the subsections that follow, EPA summarizes each step of the approach to inform an MCLG along with each decision point.

Figure [SEQ Figure * ARABIC]. Summary of Modeling Approach for Estimating Measurable Adverse Neurodevelopmental Impacts in Offspring from Perchlorate Exposure in Pregnant Woman

[EMBED Visio.Drawing.15]

9.1 Summary of BBDR Model and Decision Points (Step 1)

The BBDR model has two main components: (1) a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of these two anions; and (2) a pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, most significantly T4. The pharmacokinetic portion contains a physiological description (e.g., organ volumes, blood flows) and chemical-specific information (e.g., partition coefficients, volume of distribution, rate constants for transport, metabolism, and elimination) that enable a prediction of perchlorate and iodide internal concentration at the critical target (i.e., thyroidal sodium-iodide symporter (NIS) in association with a particular exposure scenario (route of exposure, age, dose level)). This portion of the model is similar to other PBPK models and for perchlorate is simplified by the absence of metabolism. The pharmacodynamic portion of the model uses this internal concentration to simulate how the chemical will act within a known mechanism of action to perturb host systems and lead to a toxic effect. Thus, BBDR modeling attempts to predict the internal dose of a chemical associated with a particular exposure scenario and the perturbation this internal dose can have on host systems.[18]

The BBDR model predicts serum thyroid hormone levels dependent on variables for gestational week (GW), iodine intake, TSH feedback loop strength, and perchlorate dose. The EPA aimed to model a sensitive individual in their analysis to inform the MCLG in an effort to protect the sensitive population with an adequate margin of safety, using individuals with weaker than median TSH feedback and lower than median fT4 levels. To demonstrate the output from the BBDR model for GW 13, data from which will ultimately inform the MCLG, and to demonstrate the impact of iodine intake and the strength of the TSH feedback [REF _Ref517525852 \h * MERGEFORMAT] is provided with the muted TSH feedback loop, and [REF _Ref512860812 \h * MERGEFORMAT]

[18] For additional information on the BBDR model, refer to Chapter 3 and Appendix A in the Approaches Report.

with the full TSH feedback loop. pTSH refers to the strength of the TSH feedback loop. pTSH=0.398, which is the coefficient for the muted TSH feedback loop used to produce the predictions in [REF _Ref512860801 \h], is equal to the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5 percentile value from NHANES (non-pregnant women). The full-strength TSH feedback loop used to produce the results in [REF _Ref529546636 \h] has a pTSH equal to 1.

Table [SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 for GW 13 at 75 and 170 µg/day Iodine Intake at pTSH[a] = 0.398 []

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L) (% change from 0 dose)					
	2.5th	5th	10th	50th	95th	97.5th
Iodine Intake = 170 µg/day[b]						
0	6.70	7.33	8.07	10.64	13.95	14.59
1	6.70 (-0.08%)	7.33 (-0.07%)	8.06 (-0.06%)	10.64 (-0.05%)	13.95 (-0.04%)	14.58 (-0.03%)
2	6.69 (-0.15%)	7.32 (-0.14%)	8.06 (-0.13%)	10.63 (-0.10%)	13.94 (-0.07%)	14.58 (-0.07%)
3	6.69 (-0.23%)	7.32 (-0.21%)	8.05 (-0.19%)	10.63 (-0.14%)	13.94 (-0.11%)	14.57 (-0.11%)
4	6.68 (-0.31%)	7.31 (-0.28%)	8.04 (-0.26%)	10.62 (-0.19%)	13.93 (-0.15%)	14.57 (-0.14%)
Iodine Intake = 75 µg/day[c]						
0	5.57	6.09	6.70	8.84	11.59	12.12
1	5.50 (-1.26%)	6.02 (-1.15%)	6.63 (-1.04%)	8.77 (-0.79%)	11.52 (-0.60%)	12.05 (-0.58%)
2	5.43 (-2.45%)	5.96 (-2.24%)	6.56 (-2.04%)	8.71 (-1.54%)	11.45 (-1.18%)	11.98 (-1.13%)
3	5.37 (-3.59%)	5.96 (-3.28%)	6.50 (-2.98%)	8.64 (-2.26%)	11.39 (-1.72%)	11.92 (-1.65%)
4	5.31 (-4.68%)	5.83 (-4.28%)	6.44 (-3.89%)	8.58 (-2.95%)	11.33 (-2.25%)	11.86 (-2.15%)

[a] See Section 3.1.2 for additional information on pTSH.
[b] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a standard deviation (SD) of 2.01.
[c] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 1.67.

Table [SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 for GW 13 at 75 and 170 µg/day Iodine Intake at pTSH[a] = 1

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L) (% Change from 0 Dose)					
	2.5th	5th	10th	50th	95th	97.5th
Iodine Intake = 170 µg/day[b]						
0	6.70	7.33	8.07	10.64	13.95	14.59
1	6.70 (-0.04%)	7.33 (-0.04%)	8.06 (-0.04%)	10.64 (-0.03%)	13.95 (-0.02%)	14.58 (-0.02%)
2	6.69 (-0.09%)	7.33 (-0.08%)	8.06 (-0.07%)	10.64 (-0.05%)	13.95 (-0.04%)	14.58 (-0.04%)
3	6.69 (-0.13%)	7.33 (-0.12%)	8.06 (-0.11%)	10.63 (-0.08%)	13.94 (-0.06%)	14.58 (-0.06%)
4	6.69 (-0.17%)	7.32 (-0.16%)	8.05 (-0.14%)	10.63 (-0.11%)	13.94 (-0.08%)	14.58 (-0.08%)
Iodine Intake = 75 µg/day[c]						
0	5.57	6.09	6.70	8.84	11.59	12.12
1	5.53 (-0.73%)	6.05 (-0.67%)	6.66 (-0.61%)	8.80 (-0.46%)	11.55 (-0.35%)	12.08 (-0.34%)
2	5.49 (-1.44%)	6.01 (-1.31%)	6.62 (-1.20%)	8.76 (-0.91%)	11.51 (-0.69%)	12.04 (-0.66%)
3	5.45 (-2.13%)	5.97 (-1.94%)	6.58 (-1.77%)	8.72 (-1.34%)	11.47 (-1.02%)	12.00 (-0.98%)
4	5.41 (-2.80%)	5.94 (-2.56%)	6.54 (-2.32%)	8.69 (-1.76%)	11.44 (-1.34%)	11.96 (-1.29%)

[a] See Section 3.1.2 for additional information on pTSH,
[b] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 2.01.
[c] The 50th percentile is direct output from the BBDR model, and additional percentiles are estimated by assuming a normal distribution with a SD of 1.67.

9.1.1 Iodine Intake Level and Gestational Week

The BBDR model simulates the impact of perchlorate on thyroid hormones at any level of iodine intake and at each GW from conception to week 16. Thus, EPA was required to make informed decisions as to the appropriate level of iodine intake, as well as the week of gestation for which to model perchlorate exposure for the purposes of informing the MCLG.

Individuals with low-iodine intake have increased sensitivity to the impact of perchlorate on thyroid hormone levels as the functional reserve of the hypothalamic-pituitary-thyroid (HPT) system is limited with less iodine (Leung et al., 2010). The EPA selected an iodine intake level of 75 µg/day to inform the MCLG to simulate an individual with low-iodine intake. This iodine intake level represents somewhere between the 15th and 20th percentile of the population distribution of estimated iodine intake from the NHANES. The EPA also considered conducting the MCLG analysis at the lower-iodine intake level of 50 µg/day, which represents approximately the 5th percentile of the NHANES distribution. However, at 50 µg/day of iodine intake, the BBDR model predicts TSH levels

would be elevated to within the clinically hypothyroid range before exposure to any perchlorate[19] (TSH ranges between 4.51 and 5.41 mIU/L at zero dose of perchlorate when evaluating GWs 12 or

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[19] For the purposes of this analysis, the EPA evaluated the American Thyroid Association's (ATA's) 2017 recommendations for defining hypothyroidism [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. Specifically the ATA recommends "in the pregnancy setting, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range" [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><Pages>332</Pages><DisplayText>(Alexander et al., 2017, p. 332)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. ATA goes on to state, in the absence of population- and trimester-specific reference ranges defined by a provider's institute or laboratory, that the TSH reference ranges should be obtained from similar patient populations. From their recommended studies with trimester-specific data on a U.S. population, Lambert-Meserlian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lambert-Messerlian</Author><Year>2008</Year><RecNum>100</RecNum><DisplayText>(2008)</DisplayText><record><rec-number>100</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1443808320">100</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lambert-Messerlian, Geralyn</author><author>McClain, Monica</author><author>Haddow, James E</author><author>Palomaki, Glenn E</author><author>Canick, Jacob A</author><author>Cleary-Goldman, Jane</author><author>Malone, Fergal D</author><author>Porter, T Flint</author><author>Nyberg, David A</author><author>Bernstein, Peter</author></authors></contributors><titles><title>First-and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First-and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study</title><secondary-title>American Journal of Obstetrics and Gynecology</secondary-title></titles><periodical><full-title>American journal of obstetrics and gynecology</full-title></periodical><pages>62-e1</pages><volume>199</volume><number>1</number><dates><year>2008</year></dates><publisher>Elsevier</publisher><isbn>0002-9378</isbn><urls></urls></record></Cite></EndNote>] is the largest U.S.-based population with a reference range upper bound of 3.37 mIU/L for the first trimester (and 3.35 mIU/L for the

13). In contrast, at 75 µg/day iodine, the BBDR-modeled concentrations of serum fT4 and TSH are significantly reduced from the population median but are still within the euthyroid range. This comports with the goal of evaluating perchlorate effects on the offspring of pregnant women who are borderline hypothyroxinemic on child neurodevelopment.

As previously stated, the EPA determined that modeling the first trimester would be protective of other potentially sensitive life stages. As will be described in Section [REF _Ref520707359 \r \h * MERGEFORMAT], the EPA used the Korevaar et al. (2016) study to inform the relationship between maternal fT4 and neurodevelopmental outcomes in children.[20] This study had a median gestational age of 13.2 weeks at the time of thyroid hormone collection. Therefore, the EPA selected GW 13 BBDR output for Step 1 of the analysis.

9.1.2 Strength of the TSH Feedback Loop

TSH increases in response to decreases in T4 have been captured in numerous studies that document the relationship between these hormones [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The BBDR model achieves this feedback regulation by adjusting a set of three parameters: the number of sodium-iodide symporter sites, the T4 synthesis rate, and the T3 synthesis rate. These three parameters are assumed to vary directly with the variation of the coefficient pTSH, which determines the strength of TSH stimulation. A lower bound of pTSH = 0.398 was used for the dose-response analysis to link changes in fT4 to neurodevelopmental outcomes. This assumes that sensitive individuals with high TSH and average fT4 levels exist because the stimulus strength of TSH is proportionally weaker. TSH increases can drive corresponding increases in iodide uptake and T4 and T3 production if the iodide supply is sufficient. With increasingly low-iodide intake, colloidal iodide stores are modeled to decline, which ultimately impairs the thyroid's response to elevations in TSH. The EPA chose to use a low TSH feedback coefficient to ensure protection for the sensitive population from adverse health effects.

9.1.3 Percentile of fT4

When modeling changes in fT4 due to changes in perchlorate from the BBDR model, the baseline level of fT4 affects the magnitude of changes seen as a result of perchlorate exposure. While the BBDR model can be calibrated to match specific percentiles of the population, the distributions in the underlying parameters required to predict the distribution of thyroid hormone levels have not been determined. Therefore, in order to predict the impact of perchlorate exposure on the population distribution of fT4, the EPA estimated a distribution for fT4 plasma concentrations around the median modeled values, while accounting for the effects of perchlorate and iodine. To develop population distributions for fT4 concentrations around the BBDR-estimated median fT4 values, the EPA evaluated the fT4 data from studies that were used to calibrate the BBDR model [ADDIN EN.CITE ADDIN EN.CITE.DATA].[21] The EPA assumed the variation around predicted fT4 concentrations would likely be close to normal after accounting for perchlorate and iodine intake, and

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second trimester). Therefore, these values were used to compare to BBDR output TSH values in the first trimester (or second trimester in cases of GWs 15 and 16) to determine the presence of hypothyroidism.

[20] See Section 6.3.2 of the EPA's Approaches Report for details.

[21] See Figure A-33 in Appendix A of the Approaches Report.

thus estimated a combined standard deviation (SD) using the distributional information from each of the studies [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The EPA then used the estimated combined SD to predict a distribution of fT4 around the median fT4 estimated by the BBDR model, based on particular levels of iodine sufficiency and perchlorate doses. From this distribution around the median, the EPA chose to use the 10th percentile of baseline fT4 to conduct analyses in order to model an individual with low baseline fT4 without the uncertainty of modeling effects at more extreme percentiles (e.g., 2.5th percentile) of fT4. By using the 10^{th} percentile of fT4 EPA is accounting for variability in thyroid hormones in the sensitive population.

9.2 Summary of Epidemiological Literature Connecting Changes in Maternal Thyroid Hormone Levels to Offspring Neurodevelopmental Outcomes and Decision Points (Step 2)

Data for the second step of the analysis come from epidemiological studies that evaluated maternal thyroid hormone levels in pregnancy and neurodevelopmental outcomes and not from studies evaluating perchlorate exposure. Based on recommendations of previous peer-review panels, the EPA evaluated epidemiological literature assessing the relationship between thyroid hormone levels and neurodevelopmental outcomes, regardless of the cause of hormone perturbations. As this evaluation followed the SAB recommendation, the EPA did not conduct a complete, systematic review of the body of literature and a weight-of-evidence evaluation on this topic. Instead, the EPA conducted a focused review of the published literature and identified epidemiological studies that examined thyroid hormone levels and neurodevelopmental outcomes.

9.2.1 Selection of the Approach for Step 2

Two potential methods for using the epidemiological literature to inform an MCLG were outlined in the Approaches Report. In the first proposed approach, dose-response functions were culled from the epidemiological literature (or their underlying dataset) and incremental changes in neurodevelopmental endpoints were calculated based on a given change in thyroid hormone concentration as a result of perchlorate exposure.

In the peer-reviewed report, the peer reviewers summarized the strengths and limitations of this first approach (referred to by the panel as the "two-stage" approach) as such:

> *The panel agreed that strengths of the two-stage approach include explicit linkage between perchlorate exposure and a recognized adverse effect. Although the manner in which they are linked is highly technical, it is a concept that can be readily understood, facilitating risk communication related to the MCLG. The principal limitation of this approach is the small number of studies able to contribute data to the modeling and uncertainties associated with various modeling steps* (External Peer Reviewers for U.S. EPA, 2018, p. 8).

The second proposed approach did not directly connect fT4 to neurodevelopment but instead used a distribution of fT4 to define a cut point at which hypothyroxinema occurs, and subsequently estimated the dose of perchlorate associated with a critical increase in the proportion of women predicted to be hypothyroxinemic due to perchlorate exposure. This approach was proposed based on the epidemiological evidence that early pregnancy hypothyroxinemia is a risk factor for a variety of adverse neurodevelopmental outcomes. In reviewing this approach, the peer reviewers noted the following strengths in their report:

> 1) *The central premise, that hypothyroxinemia is associated with adverse neurodevelopmental effects is supported by a large number of studies, including categorical studies; 2) This approach encompasses a variety of adverse neurodevelopmental outcomes, as indicated by these studies, rather than focusing on one or a limited number of adverse outcomes, as with the two-stage approach; and 3) This approach avoids all of the uncertainties associated with determining a quantitative relationship between a specific maternal fT4 level and the magnitude an adverse neurodevelopmental effect (External Peer Reviewers for U.S. EPA, 2018, p. 7).*

The peer reviewers expressed concern about hypothyroxinemia being a precursor effect, rather than an adverse health outcome, which they argued may create difficulties in explaining the basis for the MCLG to some audiences. However, the EPA has used precursor effects as the basis for setting regulatory and non-regulatory limits previously. The peer review panel also expressed concern that a standard definition of hypothyroxinemia has not yet been established, as clinicians use varying fT4 thresholds to define their own working definition of the condition. This also could lead to difficulties communicating the population at risk for developing this precursor effect as a result of perchlorate exposure.

Ultimately, the EPA chose to develop the MCLG using dose-response functions from the epidemiological literature to estimate neurodevelopmental impacts in the offspring of pregnant women exposed to perchlorate. EPA selected this proposed approach because it is consistent with SDWA's definition of an MCLG to avoid adverse health effects and because it is most consistent with the SAB recommendations.

9.2.2 Selection of the Dose-Response Function

As summarized in the Approaches Report, to identify studies that connected incremental changes in maternal T4 or fT4 to incremental changes in offspring neurodevelopment, the EPA assessed 71 epidemiological studies using a 4-step approach. First, studies were identified that were not compatible with BBDR model output, and these studies were not further evaluated. Next, studies were categorized depending on whether the analysis was based on a categorical or a continuous measure of thyroid hormones as they related to neurodevelopment. Because studies with continuous measures are the most useful for developing dose-response functions, they were selected over categorical studies. The studies with continuous measures of thyroid hormones that were deemed to have the potential to inform a dose-response analysis were then evaluated using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias (ROB) tool and scored. Studies that were identified as having a "definitely high risk of bias" by the ROB tool were removed from consideration. The remaining papers were evaluated to determine the feasibility of using data from the paper in a dose-response analysis.

Ultimately, the EPA focused on five studies, four related to cognition [ADDIN EN.CITE ADDIN EN.CITE.DATA] and one related to behavior [ADDIN EN.CITE <EndNote><Cite><Author>Endendijk</Author><Year>2017</Year><RecNum>1915</RecNum><DisplayText>(Endendijk, Wijnen, Pop, & van Baar, 2017)</DisplayText><record><rec-number>1915</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503500102">1915</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Endendijk,

J.J.</author><author>Wijnen, H.A.</author><author>Pop, V.J.</author><author>van Baar, A.L.</author></authors></contributors><titles><title>Maternal thyroid hormone trajectories during pregnancy and child behavioral problems</title><secondary-title>Hormones and Behavior</secondary-title></titles><periodical><full-title>Hormones and Behavior</full-title></periodical><pages>84-92</pages><volume>94</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>], which could be used to quantitatively describe how incremental changes in thyroid hormone levels in early pregnancy result in subsequent changes in neurodevelopment.[22] For each study, an analysis was conducted to evaluate the dose-response relationship between maternal thyroid hormone levels (specifically fT4) and offspring neurodevelopment. Effect estimates were either presented in the paper, or derived through the digitization of figures[23] or through novel analysis of data provided by the study authors. Each effect estimate was presented or estimated along with a 95 percent confidence interval (CI). Consistent with the EPA risk assessment policies,[24] the EPA utilized the upper effect estimate from each study to determine the dose of perchlorate associated with a given change in fT4.

Results showing the perchlorate doses associated with a 1 percent and a 2 percent change in the endpoint specific to each study of interest from its mean using the upper beta estimate, assuming the 10th percentile of baseline fT4, are presented in [REF _Ref516151019 \h * MERGEFORMAT]. These results provide a perspective on the potential impacts of perchlorate on maternal fT4 (as predicted by the BBDR model) and subsequent neurodevelopmental impacts (as predicted by the epidemiologic literature).

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[22] Detailed summaries of each study, as well as information about the EPA's independent reanalysis of the Korevaar et al. (2016) data, are presented in Chapters 5 and 6 of the Approaches Report.

[23] For any publication for which this was done EPA attempted to contact the study authors for underlying data. When these attempts were unsuccessful, the EPA opted to use the WebPlotDigitizer Extension for Google Chrome to extract the data points from the plot, along with the linear regression function in Excel to estimate a regression on the extracted data. The EPA aimed to replicate the reported R^2 values reported in the studies in order to validate the use of the WebPlotDigitizer method as a means of accurately extracting the data from the study, and were successful in doing so.

[24] The Benchmark Dose Technical Guidance document recommends the use of the 95 percent lower bound on a benchmark dose as the POD for noncancer effects, as using the lower bound accounts for the experimental variability inherent in a given study and assures (with 95 percent confidence for the experimental context) that the selected benchmark response is not exceeded (U.S. EPA, 2012).

Table [SEQ Table * ARABIC]. Predicted Dose of Perchlorate per 1 Percent to 2 Percent Change[a] in Neurodevelopmental Measure for Low-Iodine Intake Individuals Based on Upper Effect Estimates at the 10th Percentile fT4 Level[b, c]

Study	Endpoint	Dose-Response Function	β (95% CI)	ΔfT4 in pmol/L Associated with a 1% to 2% Change in Endpoint (% ΔfT4 from 0 dose perchlorate, iodine intake = 75 µg/day)[a, d]	Dose of Perchlorate per 1% to 2% Change in Endpoint (µg/kg/day)[a, d]
Korevaar et al. (2016) Quadratic	IQ	$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) - (\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$	β_1 = 33.81 (9.8, 57.82) β_2 = -6.235 (-10.567, -1.903)	-0.13 to -0.25 (1.9% to 3.8%)	1.9 to 3.9
Korevaar et al. (2016) EPA independent analysis	IQ	$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$	17.26 (3.77, 30.75)	-0.21 to -0.41 (3.1% to 6.2%)	3.1 to 6.7
Pop et al. (2003)	MDI	$\Delta MDI = \beta \times \Delta fT4$	6.3 (1.92, 10.6)	-0.09 to -0.19 (1.0% to 2.8%)	1.3 to 2.8
Pop et al. (2003)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.4 (4.0, 12.8)	-0.08 to -0.16 (0.9% to 2.4%)	1.1 to 2.3
Pop et al. (1999)	PDI	$\Delta PDI = \beta \times \Delta fT4$	8.5 (0.01, 17.0)	-0.06 to -0.12 (0.6% to 1.8%)	0.8 to 1.7
Endendijk et al. (2017)	Anxiety/ depression score	$\Delta AD = \left(\frac{1}{\beta * fT4_2}\right) - \left(\frac{1}{\beta * fT4_1}\right)$	0.12 (0.11, 0.13)	-0.03 to -0.08 (0.45% to 1.2%)	0.4 to 1.1
Finken et al. (2013)	SD of reaction time	ΔSD Reaction Time (ms) = β × Δ fT4	-4.9 (-9.5, -0.2)	-0.28 to -0.57 (4.2% to 8.5%)	4.4 to 9.8

[a] The analyses for IQ, Mental Development Index (MDI), and Psychomotor Development Index (PDI) are based on a 1% or 2% change from the standardized mean for each test, which in all instances is 100 points. The analysis for the anxiety/depression score is based on the mean score in the population (reported by sex) assessed in Endendijk et al. (2017). For a population of 51% boys, the mean anxiety/depression score is 1.18 for boys and 1.11 for girls. Thus, the EPA calculated the mean anxiety/depression score to be equal to 0.51*1.18 + 0.49*1.11 = 1.1 and calculated a 1% change (i.e., 0.01 points) and a 2% change (i.e., 0.02 points) from this value. According to communication with Endendijk et al. (2017), there is not a standardized mean for the raw scores in the Child Behavior Checklist (CBCL). The analysis for the SD of reaction time is based on the mean SD of reaction time presented in the Finken et al. (2013) paper, which was 270 ms, so a 1% change would be 2.7 ms and a 2% change would be 5.4 ms. The EPA reached out to the Finken et al. authors to confirm the standardized mean for SD of reaction time but have not received a response.

[b] This is based on the regression analysis for the range of fT4 data within each study using the upper beta estimates from the 95% CI. These results are for the low-iodide intake population of 75 µg/day. In all functions, fT4 is in units of pmol/L.

[c] The BBDR model with a pTSH of 0.398 was used for these analyses.

[d] Ranges show results from a 1% change in the endpoint from its mean value to a 2% change in the endpoint from its mean

From the seven analyses presented, the EPA chose the independent analysis of the Korevaar et al. (2016) data as the basis for calculating the POD. The reason for this selection is that a health impact function can be derived for the sensitive population of interest, adjusting for the appropriate set of confounders, with a readily interpretable endpoint.

The five identified papers evaluated a variety of endpoints with Korevaar et al. (2016) evaluating IQ, Pop et al. (1999, 2003) using the Bayley Scale to evaluate PDI and MDI, Finken et al. (2013) evaluating the SD of reaction time, and Endendijk et al. (2017) evaluating anxiety/depression scores using the CBCL. The SD of reaction time from Finken et al. (2013) was not well-received by the peer reviewers because it is difficult to ascertain the true implications of a change in the SD of reaction time. The Endendijk et al. (2017) study was identified after the peer review so no feedback was given on the appropriateness of the endpoint; however, the anxiety/depression raw score is not an intuitively interpretable endpoint. Further, neither the Endendijk et al. (2017) nor the Finken et al. (2013) analyses had functions for the sensitive life stage (i.e., their analyses were based on the full range of fT4 levels and did not concentrate on the impacts of low-end fT4 levels). For these reasons, the Endendijk et al. (2017) and Finken et al. (2013) papers were not selected for further evaluation.

The Korevaar et al. (2016) original and independent analyses are preferable compared to the Pop et al. (1999, 2003) studies because neither function derived from the Pop et al. studies was adjusted for confounders. Additionally, both Pop et al. papers have an $N < 50$ compared to the Korevaar et al. analyses, which have an N of greater than 3,600.[25]

Although the original Korevaar et al. (2016) analysis was the most rigorous analysis available in the literature to date, the Korevaar et al. (2016) EPA reanalysis was chosen over the original analysis because it included changes made to the analysis at the suggestion of the peer-review panel. The revised analysis controls for a more appropriate set of confounders, leading to more precise estimates of the association between maternal fT4 and child IQ. The EPA was prompted to revisit the original Korevaar et al. (2016) model because of the feedback received during the peer review of the Approaches Report. Specifically, a member of the peer-review panel expressed the following suggestion:

> *Korevaar et al. controlled for instrumental variables (e.g. gestational week at fT4 measurement) as well as variables that are consequences of altered fT4 (e.g. maternal BMI), which may have biased estimates. This study also assumed a log-linear relation between fT4 and the outcome but it is unclear whether the data fit this functional form better than a linear form. Reanalysis of the data performed by EPA should not include the variables noted above, which may have driven measures of association towards the null, and should investigate the most appropriate functional form to inform decisions about transformation of fT4 values* (External Peer Reviewers for U.S. EPA, 2018, pp. 61–62).

[25] The original Korevaar et al. (2016) analysis included 3,839 mother/child pairs. The EPA reanalysis of the Korevaar et al. (2016) data had a slightly lower N of 3,609, due to the exclusion of subjects with imputed values for maternal fT4.

The EPA responded to this suggestion by developing a causal model for the effect of maternal fT4 on child IQ to identify the minimum set of confounding variables, testing the proper functional form of the relationship between maternal fT4 and child IQ in the Korevaar et al. (2016) data, and making decisions about data quality and influential data points in the analysis.[26] That is, the EPA determined that there were values of the independent variable of interest, fT4, in the original analysis that were imputed using multiple imputations. This could have impacted the effect estimate of the independent variable of interest with data that were not directly measured. The EPA reanalysis excludes these non-measured values as a precaution. Subsequently, the EPA selected the Korevaar et al. (2016) reanalysis as the most appropriate function from which to assess the relationship between fT4 and IQ.

[26] The details of which are described in Section 6.3.2 of the Approaches Report.

10. Select Benchmark Response and Identify the POD

In conducting this analysis, the EPA seeks to identify an MCLG that is at a level at which no adverse neurodevelopmental impacts occur in the offspring of pregnant women who are exposed and that provides an adequate margin of safety that protect other potentially sensitive life stages from adverse health effects of perchlorate exposure. This is difficult when evaluating a continuous outcome such as IQ. Therefore, to select a dose to inform a POD, the percent change in IQ that results with no known or anticipated adverse effects needs to be defined. The EPA often uses percentage changes in noncancer risk assessment, including 5 percent or 10 percent, or a 0.5 to 1 SD change from the mean [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2012</Year><RecNum>2000</RecNum><DisplayText>(U.S. EPA, 2012)</DisplayText><record><rec-number>2000</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1529502864">2000</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Benchmark dose technical guidance</title></titles><dates><year>2012</year></dates><isbn>EPA/100/R-12/001</isbn><urls></urls></record></Cite></EndNote>]. However, these are often used when assessing toxicological data. A smaller response to inform a POD (e.g. 1%) is justified when using epidemiological literature [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2012</Year><RecNum>2000</RecNum><DisplayText>(U.S. EPA, 2012)</DisplayText><record><rec-number>2000</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1529502864">2000</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Benchmark dose technical guidance</title></titles><dates><year>2012</year></dates><isbn>EPA/100/R-12/001</isbn><urls></urls></record></Cite></EndNote>]. Given that IQ is standardized to have a mean of 100, a 1 point change would be equivalent to a 1 percent change from the standardized mean IQ.

CalEPA concluded in Carlisle et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Carlisle</Author><Year>2009</Year><RecNum>59</RecNum><DisplayText>(2009)</DisplayText><record><rec-number>59</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437145077">59</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Carlisle, J C</author><author>Dowling, K C</author><author>Siegel, D M</author><author>Alexeff, G V</author></authors></contributors><titles><title>A blood lead benchmark for assessing risks from childhood lead exposure</title><secondary-title>Journal of Environmental Science and Health</secondary-title></titles><periodical><full-title>Journal of Environmental Science and Health</full-title></periodical><pages>1200-1208</pages><volume>44</volume><number>12</number><section>1200</section><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>] that one IQ point should be considered the *de minimis* change that is appropriate for regulatory action. Specifically, Carlisle et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Carlisle</Author><Year>2009</Year><RecNum>59</RecNum><DisplayText>(2009)</DisplayText><record><rec-number>59</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

timestamp="1437145077">59</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Carlisle, J C</author><author>Dowling, K C</author><author>Siegel, D M</author><author>Alexeff, G V</author></authors></contributors><titles><title>A blood lead benchmark for assessing risks from childhood lead exposure</title><secondary-title>Journal of Environmental Science and Health</secondary-title></titles><periodical><full-title>Journal of Environmental Science and Health</full-title></periodical><pages>1200-1208</pages><volume>44</volume><number>12</number><section>1200</section><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>] argued that "while a one-point change in WISC full-scale IQ is within the standard error of an individual measurement and would not be regarded as clinical disease or cause affected individuals to seek medical care, it is still highly significant on a population basis, since a small difference…is associated with large differences in the number of children in the two tails of the IQ distribution."

Additionally, the EPA used a small change in child IQ based on epidemiological literature when considering the epidemiological evidence that linked lead exposure to IQ. Specifically, when developing the National Ambient Air Quality Standards (NAAQS) for lead, the EPA stated that "the Administrator proposed to conclude that an air-related population mean IQ loss within the range of 1 to 2 points could be significant from a public health perspective, and that a standard level should be selected to provide protection from air-related population mean IQ loss in excess of this range" [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2008</Year><RecNum>105</RecNum><Pages>6698</Pages><DisplayText>(U.S. EPA, 2008b, p. 6698)</DisplayText><record><rec-number>105</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1444079856">105</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>National ambient air quality standards for lead. 73 FR 66964. Pages 66964-67062. (November 12, 2008) (to be codified at 40. C.F.R. 51, 51, 53, and 58).</title></titles><volume>2015</volume><number>October 5</number><dates><year>2008</year></dates><urls><related-urls><url>https://www.federalregister.gov/articles/2008/11/12/E8-25654/national-ambient-air-quality-standards-for-lead</url></related-urls></urls></record></Cite></EndNote>].

For the specific context of perchlorate, the EPA is exploring avoiding both a 1 percent change and a 2 percent change in IQ as the basis for an MCLG. The corresponding Benchmark Response percent decrease in fT4 from the zero perchlorate dose baseline are 3.1% for a 1 IQ point decrease and 6.2% for a 2 IQ point decrease ([REF _Ref516151019 \h]). Combining these response rates with the results from the reanalysis of Korevaar et al. (2016) result in a POD dose of 3.1 µg/kg/day for a 1 percent change in IQ, and a POD dose of 6.7 µg/kg/day for a 2 percent change in IQ. The PODs associated with a 1 percent and a 2 percent change in IQ are likely protective of a large portion of the population not experiencing this IQ loss, given that it is based on the low end of the distribution of fT4 for a low-iodine intake population with a muted TSH feedback response. However, uncertainties in the analysis remain, as discussed in the next section.

11. Translate POD to a RfD

To use the estimated POD to estimate an RfD, the application of uncertainty factors (UFs) needs to be evaluated. This section will explore each of the EPA's UFs and provide a brief overview of the process to derive a RfD.

11.1 Consideration of Uncertainty Factors

Section 4.4.5 of *A Review of the RfD & RfC Processes* [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2002</Year><RecNum>1996</RecNum><DisplayText>(U.S. EPA, 2002)</DisplayText><record><rec-number>1996</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1527620504">1996</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>A review of the reference dose and reference concentration process</title></titles><dates><year>2002</year></dates><isbn>EPA/630/P-02/002F</isbn><urls></urls></record></Cite></EndNote>], presents the following uncertainty factors for deriving RfDs: inter-individual variability, interspecies uncertainty, extrapolating from subchronic to chronic exposure, extrapolating from a lowest-observed adverse effect level (LOAEL) rather than from a NOAEL, and an incomplete database. The EPA has considered each of these factors in deriving an RfD to inform an MCLG for perchlorate.

(1) Variation in sensitivity among the members of the human population (i.e., inter-individual variability) (uncertainty factor, within-human variability, UF_H). Section 4.4.5.3 (p 4-42) of the 2002 document states, "In general, the Technical Panel reaffirms the importance of this UF, recommending that reduction of the intraspecies UF from a default of 10 be considered only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulation(s). …Similar to the interspecies UF, the intraspecies UF can be considered to consist of a both a toxicokinetic and toxicodynamic portion (i.e. $10^{0.5}$ each)" [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2002</Year><RecNum>1996</RecNum><DisplayText>(U.S. EPA, 2002)</DisplayText><record><rec-number>1996</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1527620504">1996</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>A review of the reference dose and reference concentration process</title></titles><dates><year>2002</year></dates><isbn>EPA/630/P-02/002F</isbn><urls></urls></record></Cite></EndNote>].

   a. *Applicable.* The inter-individual variation in the NIS structure and/or regulation contributing to variance across the population in the impact of perchlorate exposure on thyroid function is currently unknown. Although the BBDR model does its best to model the relationship between perchlorate and fT4 in the identified sensitive population of first trimester fetuses, there is still uncertainty due to the lack of data, as explained in the Approaches Report [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2018</Year><RecNum>1995</RecNum><DisplayText>(U.S. EPA, 2018)</DisplayText><record><rec-number>1995</rec-number><foreign-keys><key

app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1527619441">1995</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Proposed approaches to inform the derivation of a maximum contaminant level goal for perchlorate in drinking water</title></titles><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]:

"On the pharmacokinetic side of the model…. there are very few calibration data for perchlorate kinetics in humans, particularly at the life stage of interest. This may be of particular importance given that available biomarker data to relate perchlorate external dose to internal serum concentration are highly variable and uncertain. For example, the Lumen et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Fisher</Author><Year>2013</Year><RecNum>249</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>249</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468416440">249</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fisher, J</author><author>Li, S.</author><author>Crofton, K.</author><author>Zoeller, R. T.</author><author>McLanahan, E. D.</author><author>Lumen, A.</author><author>Gilbert, M. E.</author></authors></contributors><auth-address>U.S. Food and Drug Administration, National Center for Toxicological Research, Jefferson, AR, USA. jeffrey.fisher@fda.hhs.gov</auth-address><titles><title>Evaluation of iodide deficiency in the lactating rat and pup using a biologically based dose-response model</title><secondary-title>Toxicol Sci</secondary-title></titles><periodical><full-title>Toxicol Sci</full-title></periodical><pages>75-86</pages><volume>132</volume><number>1</number><edition>2013/01/05</edition><keywords><keyword>Animals</keyword><keyword>Calibration</keyword><keyword>Deficiency Diseases/ physiopathology</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Hypothalamo-Hypophyseal System</keyword><keyword>Iodides/ metabolism</keyword><keyword>Lactation</keyword><keyword>Models, Biological</keyword><keyword>Rats</keyword><keyword>Thyroid Gland/physiopathology</keyword><keyword>Thyroid Hormones/blood</keyword></keywords><dates><year>2013</year><pub-dates><date>Mar</date></pub-dates></dates><isbn>1096-0929 (Electronic)
1096-0929 (Linking)</isbn><accession-num>23288054</accession-num><urls></urls><electronic-resource-num>10.1093/toxsci/kfs336</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] model was based on pregnant women living in a Chilean city with high levels of perchlorate in drinking water [ADDIN EN.CITE ADDIN EN.CITE.DATA]. In that study, the standard deviation of the concentration of perchlorate in urine was similar to, or in one instance, greater than the mean urinary perchlorate concentration, indicating

extreme variability. Furthermore, data used in the calibration from the Chilean city in Telléz Telléz et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] did not reflect a low-iodine intake population. Urinary iodide for the 37 subjects at the second prenatal visit was, on average, 217 µg/L, with a standard deviation of 109 µg/L" (p. 3-16).

In addition, "toxicodynamic aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. … The degree to which there is inter-individual variation in NIS structure and/or regulation contributing to variance across the population in the impact of perchlorate exposure on thyroid function is currently unknown. … Given the limited data available for model evaluation, perchlorate toxicokinetics and toxicodynamics in pregnancy remain a source of uncertainty. This could impact the resulting fT4 predictions of neurodevelopmental effects" (p. 3-18).

There are also uncertainties in linking maternal fT4 levels to an offspring's IQ. These uncertainties include the population for which dose-response information is available (i.e., no study is U.S.-based), a lack of study information on the iodine intake status for the population for which the dose-response information is available, uncertainties around the methods used to assess maternal fT4 measurement during pregnancy, and uncertainties related to the true distribution of fT4 for a given iodine intake.[27]

Although human data were used to calibrate the BBDR model, these data are not specific to the most sensitive individuals (i.e., the fetuses of hypothyroxinemic pregnant women). Further, as outlined in Section 2, the EPA believes that protecting the fetus of a hypothyroxinemic woman will protect other identified sensitive life stages. However, there is some uncertainty due to the lack of information linking incremental changes in infant thyroid hormone levels to adverse neurodevelopmental outcomes.

Subsequently, the EPA has determined that it is appropriate to employ an uncertainty factor of 3. The value of 3 was selected instead of the full 10 because the EPA has specifically attempted to model the most sensitive individuals (i.e., muted TSH feedback, low fT4 values, low-iodine intake). However, as outlined above, there remains important pieces of data which are still uncertain. Therefore, a UF of 3 is necessary to ensure protection of the most vulnerable populations with an adequate margin of safety and to account for differences at other life stages (e.g., bottle-fed vs. breast-fed infants).

(2) Uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty) (uncertainty factor, animal-to-human, UF_A)

a. *Not applicable.* Animal studies were not used to develop the BBDR model nor were they used to relate alternations in maternal fT4 to IQ. Therefore, the EPA assigns this UF a value of 1.

[27] For more details, see Section 6.5 in the Approaches Report.

(3) Uncertainty in extrapolating data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure) (uncertainty factor, subchronic to subchronic, UF_S)

a. *Not applicable.* Extrapolating from subchronic to chronic exposures did not occur given that the BBDR model was "designed to assess long-term steady-state conditions in the non-pregnant woman and week-to-week variation in pregnancy, rather than short-term (hour-to-hour or day-to-day) fluctuations" (U.S. EPA, 2018, p. 3-3). Therefore, the EPA assigns this UF a value of 1.

(4) Uncertainty in extrapolating from a LOAEL rather than from a NOAEL (uncertainty factor, LOAEL-to-NOAEL, UF_L)

a. *Not applicable.* LOAELs and NOAELs were not identified or used in this approach. Therefore, the EPA assigns this UF a value of 1.

(5) A database UF is applied, when needed, to address the potential for deriving an inadequately protective RfD in the instance where the available database is incomplete as a result of an incomplete characterization of the chemical's toxicity (uncertainty factor, database deficiency, UF_D) US EPA, 2002).

a. *Not applicable.* As described in Section 2.4 of the SAB stated, "the mode of action of perchlorate toxicity is well understood" (SAB, 2013, p. 2) Based on the findings of a 2005 NAS report, the EPA has previously concluded that a UF_D was not needed for deficiencies in the perchlorate database (NRC, 2005; US EPA, 2005) . Therefore, the EPA assigns a UF_D value of 1.

11.2 RfD

Using the POD of 3.1 µg/kg/day based on a 1 percent change in the standardized mean IQ from the EPA's independent analysis of the Korevaar et al. (2016) data (Section [REF _Ref516142958 \r \h]), the EPA can derive an RfD by incorporating the UF_H. This results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{3.1}{3} = 1.03 \frac{\mu g/kg}{day}$$

Using the POD of 6.7 µg/kg/day based on a 2 percent change in the standardized mean IQ from the EPA's independent analysis of the Korevaar et al. (2016) data (Section [REF _Ref516142958 \r \h]), the EPA can derive a second RfD by incorporating the UF_H, which results in the following:

$$RfD = \frac{POD}{UF_H} = \frac{6.7}{3} = 2.23 \frac{\mu g/kg}{day}$$

12. Translate RfD to a Drinking Water Equivalent Level and Identify the MCLG

To translate the RfD (µg/kg/day) to an MCLG in drinking water (µg/L), the EPA will use the following equation:

$$W\left(\frac{\mu g}{L}\right) = \frac{RfD}{DWI} \times RSC_w$$

where:

W = drinking water concentration of perchlorate;

RfD = reference dose (1.03 µg/kg/day for a 1 percent change or 2.23 µg/kg/day for a 2 percent change in IQ);

DWI = bodyweight-adjusted drinking water ingestion rate (L/kg/day); and

RSC_w = relative source contribution.

This section walks the reader through each input in the above equation (with the exception of the RfD derivation, which was described previously) and presents a justification for its use in estimating an MCLG for perchlorate in drinking water.

12.1 Drinking Water Intake

Given the above equation for translating the RfD to a concentration, it is necessary to determine the most appropriate bodyweight-adjusted drinking water ingestion rate for the target population of first-trimester pregnant women. The EPA Exposure Factors Handbook (EFH) [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1740</RecNum><DisplayText>(U.S. EPA, 2011b)</DisplayText><record><rec-number>1740</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206447">1740</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Exposure factors handbook: 2011 edition (final)</title></titles><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment</publisher><isbn>EPA/600/R-090/052F</isbn><label>786546</label><work-type>EPA Report</work-type><urls><related-urls><url>http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>] reports mean, 90th, and 95th percentile bodyweight-adjusted drinking water intakes for pregnant, lactating, and non-pregnant non-lactating women of childbearing age from the [HYPERLINK \l "_ENREF_62" \o "Kahn, 2008 #2002"] study based on the Continuing Survey of Food Intakes by Individuals (CSFII) data from 1994 to 1996 and 1998. This study estimated bodyweight-adjusted drinking water intake rates for direct and indirect community water ingestion, as well as for direct and indirect water intake from all sources, on both a per-capita and consumers-only basis. As the proposed MCLG is specific for the offspring of pregnant women consuming community drinking water, the EPA chose to focus on community drinking water

intake estimates on a consumers-only basis as potential inputs. These estimates are reported in Table 3-81 in EFH [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1740</RecNum><DisplayText>(U.S. EPA, 2011b)</DisplayText><record><rec-number>1740</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206447">1740</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Exposure factors handbook: 2011 edition (final)</title></titles><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment</publisher><isbn>EPA/600/R-090/052F</isbn><label>786546</label><work-type>EPA Report</work-type><urls><related-urls><url>http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>] and are reproduced in [REF _Ref517280964 \h].

Table [SEQ Table * ARABIC]. Consumers-Only Estimated Direct and Indirect Community Water Ingestion Rates from Kahn and Stralka (2008) (L/kg/day)

Women Categories	Sample Size	Mean	90th Percentile	95th
Pregnant	65	0.014[a]	0.033[a]	
Lactating	33	0.026[a]	0.054[a]	
Non-pregnant, non-lactating, 15 to 44 years of age	2,028	0.015	0.032	

[a] The sample size does not meet minimum reporting requirements to make statistically reliable estimates as described in the *Third Report on Nutrition Monitoring* 1994-1996 [ADDIN EN.CITE <EndNote><Cite><Author>FASEB/LSRO</Author><Year>1995</Year><RecNum>2003</RecNum><DisplayText>1995)</DisplayText><record><rec-number>2003</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1529955869">2003</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>FASEB/LSRO</author></authors></contributors><titles><title>Third report monitoring in the United States</title></titles><volume>1</volume><dates><year>1995</year></dates><pub-locatio DC</pub-location><urls><related-urls><url><style face="underline" font="default" size="100%">https://www.cdc.gov/nchs/data/misc/nutri95_1acc.pdf</style></url></related-urls></urls></record></Cite></EndNote>].

The EPA chose to use exposure factor estimates specific to women of childbearing age in deriving an MCLG (i.e., non-pregnant, non-lactating, 15–44 years of age). This determination was reached as the analysis in the development of an RSC was performed using a population of women of childbearing age from NHANES (20 – 44 years of age). The EPA acknowledges there is a difference in the age group defining women of child bearing age used to develop the drinking water intake rate compared to what is used to develop the relative source contribution, which was based on the age group used in developing the BBDR model. However, the EFH reports this drinking water intake to be applicable for women of childbearing age, and the age range of the BBDR model fits within the age range used to estimate this recommended drinking water intake. Subsequently the Agency believes the difference in the age groups will have minimal impact on the resulting MCLG analysis. The EPA has chosen to apply the 90th percentile drinking water intake rate, in order to account for variability in drinking

water intakes. Thus, according to Table 3-81 in the EFH [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>1740</RecNum><DisplayText>(U.S. EPA, 2011b)</DisplayText><record><rec-number>1740</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206447">1740</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Exposure factors handbook: 2011 edition (final)</title></titles><dates><year>2011</year></dates><pub-location>Washington, DC</pub-location><publisher>U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment</publisher><isbn>EPA/600/R-090/052F</isbn><label>786546</label><work-type>EPA Report</work-type><urls><related-urls><url>http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252</url></related-urls></urls><language>English</language><modified-date>U.S. Environmental Protection Agency</modified-date></record></Cite></EndNote>] the bodyweight-adjusted drinking water intake rate for women of childbearing age is 0.032 L/kg/day.

12.2 Relative Source Contribution

The EPA believes that dietary ingestion is the only significant pathway for non-drinking-water perchlorate exposure. Thus, EPA estimates the RSC for drinking water, or the percentage of the RfD that is left for drinking water when accounting for all other routes of exposure, from the following equation:

$$RSC = \frac{RfD - Food}{RfD} \times 100\%$$

In order to estimate the RSC from this equation, it was necessary to produce an estimate for the dose of perchlorate coming from food in women of childbearing age. To estimate this figure the EPA mimic the approach taken by Abt et al. (2016; See Section [REF _Ref530562089 \r \h]). However, for the purposes of estimating perchlorate dose for informing the MCLG, the EPA also wanted to obtain distributional information on perchlorate in food, such as the 95th percentile intake rate for women of childbearing age. Additionally, the EPA examined the same age group that was used in the BBDR model for other parameters, to match the perchlorate doses from the BBDR model. The EPA produced these estimates by following the methods for estimating perchlorate consumption that were published in Abt et al. (2016), and subsequently summarized distributional information for perchlorate in food, specifically for the same age group used in the BBDR model for other parameters (women 20 to 44 years of age).

To begin EPA combined data from the following sources:

- The NHANES is run by the Centers for Disease Control and Prevention's National Center for Health Statistics and was designed to collect information on the health and nutritional status of the U.S. civilian, non-institutionalized population through in-home interviews and physical examinations [ADDIN EN.CITE <EndNote><Cite><Author>CDC</Author><Year>2007-2008, 2009-2010, 2011-2012</Year><RecNum>2005</RecNum><DisplayText>(CDC & NCHS, 2007-2008, 2009-2010, 2011-2012)</DisplayText><record><rec-number>2005</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530038652">2005</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>CDC,</author><author>NCHS</author></authors></con

tributors><titles><title>National health and nutrition examination survey data</title></titles><dates><year>2007-2008, 2009-2010, 2011-2012</year></dates><urls><related-urls><url>http://www.cdc.gov/nchs/nhanes.htm</url></related-urls></urls></record></Cite></EndNote>].

- What We Eat in America (WWEIA) provides 24-hour food diary data that are collected as part of NHANES and serves as the dietary intake measurement component of the survey. Dietary data are collected for up to two days for each respondent [ADDIN EN.CITE <EndNote><Cite><Author>CDC</Author><Year>2007-2008, 2009-2010, 2011-2012</Year><RecNum>2005</RecNum><DisplayText>(CDC & NCHS, 2007-2008, 2009-2010, 2011-2012)</DisplayText><record><rec-number>2005</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530038652">2005</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>CDC,</author><author>NCHS</author></authors></contributors><titles><title>National health and nutrition examination survey data</title></titles><dates><year>2007-2008, 2009-2010, 2011-2012</year></dates><urls><related-urls><url>http://www.cdc.gov/nchs/nhanes.htm</url></related-urls></urls></record></Cite></EndNote>].
- The Food and Drug Administration's (FDA's) Total Diet Study (TDS) is an ongoing FDA program that collects information on levels of various contaminants, including perchlorate, which occur in food and beverages commonly consumed by the U.S. population [ADDIN EN.CITE <EndNote><Cite><Author>U.S. FDA</Author><Year>2015</Year><RecNum>2006</RecNum><DisplayText>(U.S. FDA, 2015)</DisplayText><record><rec-number>2006</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530038884">2006</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>U.S. FDA,</author></authors></contributors><titles><title>Total diet study — study design</title></titles><dates><year>2015</year></dates><urls><related-urls><url>http://www.fda.gov/food/foodscienceresearch/totaldietstudy/ucm184232.htm#</url></related-urls></urls></record></Cite></EndNote>]. To estimate the levels of contaminants in these food products, the FDA buys these foods as a consumer would, prepares them as directed,[28] and then analyzes the prepared foods for levels of the contaminants of interest. This process yields nationally representative estimates of contaminant levels in more than 280 kinds of food and beverages.

The analysis plan followed by the EPA to estimate food consumption estimates can be divided into eight main steps:

1. Aggregate TDS data cycles from 2008 to 2012 to maximize the samples of perchlorate contaminants in food.
2. Account for values of perchlorate that fall below the level of detection (LOD).

[28] The FDA prepares their samples using deionized water.

3. Aggregate WWEIA data cycles from 2007 to 2012 to maximize the number of women of childbearing age with consumption data.
4. Match the Xue, Zartarian, Wang, Liu, & Georgopoulos,[ADDIN EN.CITE ADDIN EN.CITE.DATA] method and the World Health Organization (WHO) method [ADDIN EN.CITE <EndNote><Cite><Author>European Food Safety Authority</Author><Year>2010</Year><RecNum>2007</RecNum><DisplayText>(Authority, 2010)</DisplayText><record><rec-number>2007</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530039022">2007</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>European Food Safety Authority</author></authors></contributors><titles><title>Management of left-censored data in dietary exposure assessment of chemical substances</title><secondary-title>EFSA Journal</secondary-title></titles><periodical><full-title>EFSA Journal</full-title></periodical><pages>1-96</pages><number>8</number><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>] that summarize TDS lead exposure data (95th percentile lead levels in each food) to WWEIA consumption data for those foods using the matching file obtained on May 26, 2017 from FDA. This is the same matching file that was used in Abt et al. (2016).
5. Create summary perchlorate consumption information from the WWEIA/TDS data file, based on those women with two days of dietary data.
6. Aggregate the NHANES demographic data to correspond with the WWEIA participants.
7. Merge the summary perchlorate consumption information with the NHANES demographic variables.
8. Estimate the relevant summary statistics.

Multiple years of TDS data on perchlorate in food are available from FDA. The EPA combined perchlorate in food data collected in TDS for the years spanning 2008–2012. With four samples taken for each food for each year of data, the EPA had a total of 20 perchlorate samples for each of the 282 foods in the TDS. To account for non-detects in the TDS data, the EPA used three methods when summarizing the data for each food. The EPA first used a method suggested by WHO to calculate both the lower and upper bound concentrations in the foods by substituting all values below the LOD with zero to estimate the lower bound, and substituting all values below the LOD with the LOD to estimate the upper bound [ADDIN EN.CITE <EndNote><Cite><Author>European Food Safety Authority</Author><Year>2010</Year><RecNum>2007</RecNum><DisplayText>(Authority, 2010)</DisplayText><record><rec-number>2007</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530039022">2007</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>European Food Safety Authority</author></authors></contributors><titles><title>Management of left-censored data in dietary exposure assessment of chemical substances</title><secondary-title>EFSA Journal</secondary-title></titles><periodical><full-title>EFSA Journal</full-title></periodical><pages>1-96</pages><number>8</number><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. This method was used for the perchlorate analysis conducted in Abt et al. (2016). Additionally, the EPA used an approach based on Xue et al. (2010), which assigns half the LOD to values below the LOD if there is at least one detection among the multiple samples taken of each commodity; otherwise a value of zero is assigned. The WHO lower and upper bounds provide bounding on the summarized perchlorate concentration estimates calculated from the TDS data; and

results calculated with other substitution methods to account for the non-detects, including the Xue LOD method, would fall within these bounds.

The EPA calculated both the mean and the 95th percentile of the perchlorate levels in each food based on the TDS data. In order to estimate the 95th percentile from the 20 samples of each food in the TDS data, the EPA used the second-highest test result in each food to represent the 95th percentile concentration. While simple, this method avoids the need to assume a distributional shape for the samples, and has been used in recent publications of TDS data for iodine [ADDIN EN.CITE <EndNote><Cite><Author>Carriquiry</Author><Year>2016</Year><RecNum>2008</RecNum><DisplayText>(Carriquiry et al., 2016)</DisplayText><record><rec-number>2008</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1530039524">2008</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Carriquiry, A. L. </author><author>Spungen, J. H.</author><author>Murphy, S. P.</author><author>Pehrsson, P. R.</author><author>Dwyer, J. T.</author><author>Juan, W.</author><author>Wirtz, M. S. </author></authors></contributors><titles><title>Variation in the iodine concentrations of foods: considerations for dietary assessment</title><secondary-title>The American Journal of Clinical Nutrition</secondary-title></titles><periodical><full-title>The American Journal of Clinical Nutrition</full-title></periodical><pages>877S–887S</pages><number>104(Suppl 3)</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].

In order to understand food consumption patterns in women of child-bearing age, the EPA combined WWEIA food diary data from 2007 to 2012 into one large dataset to maximize the number of women. These food diary data include each individual food that was consumed during each 24-hour study period, as well as the amount of each food consumed measured in grams. For a large subset of respondents, food diary data are available for two days. For this analysis, the EPA included only participants with two days of dietary survey data and used the appropriate NHANES survey weights for this segment of the dataset.

The EPA then matched each food consumed with both its mean and its estimated 95th percentile perchlorate contamination amount from the TDS. Foods that are included in the TDS are not characterized and coded the same way as the foods in the WWEIA food diaries. Therefore, it is necessary to use expert judgement to match the TDS foods with the WWEIA foods. The study authors of Abt et al. (2016) provided the EPA with a TDS/WWEIA matching file[29] that is relevant for the years 2003–2012.[30] For this reason, the EPA did not include the most recent WWEIA data (2013–2014) in the analysis as some of the WWEIA food codes have changed since the creation of the mapping file.

Using the Abt et al. (2016) matching file, the EPA matched relevant TDS perchlorate contamination information with each food present in the WWEIA consumption data. The EPA then calculated each participant's daily perchlorate ingestion by estimating the average of the two days of estimated

[29] The matching file, "TDSMapping_2003-2012.xlsx," was emailed to EPA by Judith Spungen of FDA on May 26, 2017.

[30] The development of the mapping file relied on some expert judgement by FDA as it relates to matching food groups and consumption data.

perchlorate consumption. The EPA divided each NHANES participant's estimated daily perchlorate consumption estimate by their individual-specific bodyweight to arrive at their individual bodyweight adjusted daily perchlorate consumption. The EPA then calculated perchlorate consumption distributional information from these individual bodyweight adjusted daily perchlorate intakes.

The EPA first replicated the mean food consumption results in Abt et al. (2016), matching the mean perchlorate consumption estimates using WHO lower and upper bounds reported in the paper (using the mean value for each food from TDS). The EPA then restricted the sample to only include women 20 to 44 years of age in order to focus on women of childbearing age. To estimate the food consumption distributional information, the EPA paired both the mean and the 95th percentile estimates of perchlorate in food from the TDS with the food consumption data based on the two-day intake diaries in WWEIA, and adjusted for each individual's bodyweight to produce the estimates in [REF _Ref517684101 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. Perchlorate Consumption from Food (µg/kg/day) in U.S. Women Aged 20–44 Using the Mean and 95th Percentile TDS Results[a]

Level of Bodyweight Adjusted Perchlorate Consumption from Population Distribution	Perchlorate Dose in Food Based on Mean Concentrations of TDS data (µg/kg/day)	Perchlorate Dose in Food Based on 95th Percentile Concentrations of TDS data (µg/kg/day)
Mean	0.09–0.12	0.23–0.24
50th Percentile	0.08–0.10	0.17–0.19
90th Percentile	0.18–0.21	**0.45**
95th Percentile	0.23–0.26	0.59–0.60
97.5 Percentile	0.27–0.30	0.80–0.81
99th Percentile	0.33–0.38	1.16–1.17

[a] Ranges are due to various approaches for handling values < LOD. If no range is presented, all approaches resulted in the same value.
The **bolded** value represents the selected value

Given these results, the EPA chose to use the 90th percentile bodyweight-adjusted perchlorate consumption from food using the 95th percentile TDS results to estimate the perchlorate RSC from drinking water. The EPA believes this is the most appropriate value for perchlorate consumption from food to ensure the protection of potentially highly exposed individuals. Given the range of perchlorate concentrations in food, and that food is the only other exposure source being considered in the RSC analysis, the EPA believes it is sufficiently protective to estimate the MCLG for drinking water using the 90th percentile bodyweight-adjusted perchlorate consumption based on the 95th percentile concentrations in TDS. This assures that highly exposed individuals from this most sensitive population are considered in the evaluation of whether perchlorate is found at levels of health concern.

The RSC from drinking water can be calculated as follows by using a 1 percent change in IQ as the basis for the RfD:

$$RSC = \frac{1.03 - 0.45}{1.03} \times 100\% = 56\%,$$

or a 2 percent change in IQ as the basis for the RfD:

$$RSC = \frac{2.23-0.45}{2.23} \times 100\% = 80\%.$$

Using these RSCs in the standard equation to develop the MCLG, along with the previously used bodyweight-adjusted drinking water intake rate for women of childbearing age of 0.032 L/kg/day, results in the following estimates for the MCLG:

$$W\left(\frac{\mu g}{L}\right) = \frac{RfD\ (\mu g/kg/day)}{DWI\ (L/kg/day)} \times RSC_w.$$

A 1 percent change in IQ as the basis for the RfD results in:

$$W\left(\frac{\mu g}{L}\right) = \frac{1.03\ \mu g/kg/day}{0.032\ L/kg/day} \times 56\% = 18.03\ \mu g/L.$$

A 2 percent change in IQ as the basis for the RfD results in:

$$W\left(\frac{\mu g}{L}\right) = \frac{2.23\ \mu g/kg/day}{0.032\ L/kg/day} \times 80\% = 55.7\ \mu g/L.$$

12.3 Evaluation of Uncertainty and Variability in the MCLG

As indicated throughout this document, each input into the analysis to inform the MCLG is a decision point. The EPA has attempted to select the most appropriate inputs to protect the most sensitive population with an adequate margin of safety. Specifically, the EPA evaluated both a 1 percent and a 2 percent change in IQ. The EPA conducted analyses to determine the effect that varying specific inputs will have. The EPA tested the effect of varying the drinking water intake by assuming the drinking water intake rate for pregnant women, or 0.033 L/kg/day. The EPA also evaluated the impact of using the median fT4 estimates to inform the POD as opposed to the 10th percentile. The following subsections will demonstrate some of the uncertainty and variability in the resulting MCLG values based on varying inputs, considering a 1 percent and a 2 percent change in IQ.

12.3.1 Using a POD for a 1 Percent Change in IQ

When considering a POD based on a 1 percent change in IQ, the EPA used the following inputs to calculate the MCLG:

- POD = 3.1 µg/kg/day, based on BBDR model output from the thirteenth week of gestation, pTSH = 0.398, at 75 µg/day iodine intake, at the 10th percentile of baseline fT4, matched with the function relating changes in maternal fT4 to child IQ from the EPA reanalysis of Korevaar et al. (2016).[31]
- RSC = 56 percent, based on subtracting the 90th percentile of perchlorate ingestion from food from the calculated RfD of 1.03 µg/kg/day based on the 3.1 µg/kg/day POD, assuming the 95th percentile concentration of perchlorate in each food.
- Uncertainty factor = 3, to account for intraspecies variability in sensitivity to perchlorate.

[31] For justification, see Section [REF _Ref529865790 \r \h].

- Drinking water ingestion (DWI) = 0.032 L/kg/day, based on the 90th percentile of consumers-only bodyweight-adjusted direct and indirect community drinking water intake for women of childbearing age from Kahn and Stralka (2008), as presented in Table 3-81 of the EFH (2011).

If using the median fT4 values, the POD would be equal to 4.2 µg/kg/day based on the EPA's independent analysis of the Korevaar et al. (2016) data (Section [REF _Ref515367288 \r \h]) and, thus, the RfD would equal 1.40 µg/kg/day after applying the UF of 3. The RSC based on this new RfD of 1.40 µg/kg/day would be 68 percent, based on subtracting the 90th percentile of perchlorate ingestion from food from the RfD, assuming the 95th percentile concentration of perchlorate in each food. The impact of varying each of these parameters is summarized in [REF _Ref530562482 \h].

Table [SEQ Table * ARABIC]. Impact of Selecting Various fT4 Percentiles and DWI Rates on Inputs, and Calculated MCLG Based on a 1 Percent Change in IQ

	MCLG	
	10th Percentile fT4	50th Percentile fT4
MCLG using women of childbearing age DWI (0.032 L/kg/day)	**18.0**	29.8
MCLG using pregnant women DWI (0.033 L/kg/day)	17.5	28.9
Inputs		
POD (µg/kg/day)	3.1	4.2
RfD (µg/kg/day)	1.03	1.40
RSC	56%	68%
The **bolded** value indicates the selected value.		

12.3.2 Using a POD for a 2 Percent Change in IQ

When considering a POD based on a 2 percent change in IQ, the EPA used the following inputs to calculate the MCLG:

- POD = 6.7 µg/kg/day, based on the BBDR model output from the thirteenth week of gestation, pTSH = 0.398, at 75 µg/day iodine intake, at the 10th percentile of baseline fT4, matched with the function relating changes in maternal fT4 to child IQ from the EPA reanalysis of Korevaar et al. (2016).[32]
- RSC = 80 percent, based on subtracting the 90th percentile of perchlorate ingestion from food from the calculated RfD of 2.23 µg/kg/day, based on the 6.7 µg/kg/day POD, assuming the 95th percentile concentration of perchlorate in each food.
- Uncertainty factor = 3, to account for intraspecies variability in sensitivity to perchlorate.
- DWI = 0.032 L/kg/day, based on the 90th percentile of consumers-only bodyweight-adjusted direct and indirect community drinking water intake for women of childbearing age from Kahn and Stralka (2008), as presented in Table 3-81 of the EFH (2011).

If using the median fT4 values, the POD would be equal to 9.3 µg/kg/day based on the EPA's independent analysis of the Korevaar et al. (2016) data (Section [REF _Ref515367288 \r \h * MERGEFORMAT]) and, thus, the RfD would equal 3.10 µg/kg/day after applying the UF of 3. The RSC, based on this new RfD of 3.10 µg/kg/day would be 80 percent, as subtracting the 90th

[32] For justification, see Section [REF _Ref529865904 \r \h].

percentile of perchlorate ingestion from food from the RfD, assuming the 95th percentile concentration of perchlorate in each food yields an RSC of 85 percent, which is greater than the EPA suggested RSC "ceiling" of 80 percent [ADDIN EN.CITE <EndNote><Cite><Author>EPA</Author><Year>2000</Year><RecNum>2026</RecNum><DisplayText>(U.S. EPA, 2000)</DisplayText><record><rec-number>2026</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1539631152">2026</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000)</title></titles><dates><year>2000</year></dates><pub-location>Washington, DC</pub-location><isbn>EPA-822-B-00-004</isbn><urls><related-urls><url>https://www.nj.gov/drbc/library/documents/EPA_human-health-criteria2000.pdf</url></related-urls></urls></record></Cite></EndNote>]. The impact of varying each of these parameters is summarized in [REF _Ref519031384 \h * MERGEFORMAT].

Table [SEQ Table * ARABIC]. Impact of Selecting Various fT4 Percentiles and DWI Rates on Inputs, and Calculated MCLG Based on a 2 Percent Change in IQ

	MCLG	
	10th Percentile fT4	50th Percentile fT4
MCLG using women of childbearing age DWI (0.032 L/kg/day)	**56**	78
MCLG using pregnant women DWI (0.033 L/kg/day)	54	75
Inputs		
POD (µg/kg/day)	6.7	9.3
RfD (µg/kg/day)	2.23	3.10
RSC	80%	80%[a]

[a] For a 2 IQ point change at the 50th percentile fT4 the calculated RSC is 85%. The EPA therefore applied the 80% "ceiling" instead of this calculated value

The **bolded** value indicates the selected value.

[REF _Ref530562482 \h] and [REF _Ref519031384 \h] show that the selected DWI rate has very little impact on the estimated MCLG. Using the median fT4 value results in a higher POD, a higher RSC, and subsequently also higher potential MCLGs. Since the EPA is aiming to protect the most sensitive population, the use of the lower percentile fT4 value is appropriate.

12.4 Conclusion

The EPA identified potential MCLGs for perchlorate in drinking water in the range of 18.0 µg/L to 56 µg/L, informed by an evaluation using the best available peer-reviewed science and methods.

13. References

[ADDIN EN.REFLIST]

United States
Environmental Protection
Agency

Health Risk Reduction and Cost Analysis of the Proposed Perchlorate National Primary Drinking Water Regulation

Office of Water (4607M)
EPA XXX-X-XX-XXX
January 2019
[HYPERLINK "http://www.epa.gov/safewater"]

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Table of Exhibits

[TOC \t "Caption" \c]

Abbreviations and Acronyms

ACS	American Community Survey
ADHD	attention-deficit/hyperactive disorder
Agency	U.S. Environmental Protection Agency
ANSI	American National Standards Institute
ASES	Annual Social and Economic Supplement
BBDR	biologically based dose response
BLS	Bureau of Labor Statistics
CCL	Contaminant Candidate List
CCR	Consumer Confidence Report
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
Council	National Drinking Water Advisory Council
CPS	Current Population Survey
CSFII	Continuing Survey of Food Intakes by Individuals
CVD	cardiovascular disease
CWS	community water system
CWSS	Community Water System Survey
DWI	drinking water intake
EFH	Exposure Factors Handbook
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
fT4	free thyroxine
GW	gestational week
HRL	Health Reference Level
HRRCA	Health Risk Reduction and Cost Analysis
ICC	intraclass correlation coefficient
IQ	intelligence quotient
LDL	low-density lipoprotein
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MHI	mean household income
µg/day	micrograms per day
µg/kg/day	micrograms per kilogram per day
µg/L	micrograms per liter
MGD	million gallons per day
MOA	mode of action
MRL	minimum reporting level
NCES	National Center for Education Statistics
NCOD	National Contaminant Occurrence Database
NCWS	non-community water system
NDWAC	National Drinking Water Advisory Council
NHANES	National Health and Nutrition Examination Survey
NIS	sodium-iodide symporter
NLSY	National Longitudinal Survey of Youth

NPDWR	national primary drinking water regulation
NRC	National Research Council
NSF	National Science Foundation
NTNCWS	non-transient non-community water system
NTTAA	National Technology Transfer and Advancement Act
O&M	operating and maintenance
OMB	Office of Management and Budget
ClO_4^-	Perchlorate
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic
pmol/L	picomoles per litre
POTW	publicly owned treatment works
POU	point-of-use
pph	persons per household
PUMS	Public Use Microdate Sample
PWS	public water system
RFA	Regulatory Flexibility Act
RfD	reference dose
SAB	Science Advisory Board
SBA	Small Business Administration
SBREFA	Small Business Regulatory Enforcement Fairness Act
SDWA	Safe Drinking Water Act
SDWIS	Safe Drinking Water Information System
SDWIS/FED	Federal Safe Drinking Water Information System
SSA	Social Security Administration
SSCT	small system compliance technology
T3	triiodothyronine
T4	thyroxine
TNCWS	transient non-community water system
TSH	thyroid stimulating hormone
UCMR	Unregulated Contaminant Monitoring Rule
UCMR 1	Unregulated Contaminant Monitoring Rule (first)
UMRA	Unfunded Mandates Reform Act
WBS	work breakdown structure

1 Introduction

The U.S. Environmental Protection Agency (EPA or the Agency) is proposing to regulate perchlorate in drinking water distributed by certain public water systems (PWSs). In 2011, the EPA determined that a national primary drinking water regulation (NPDWR) for perchlorate would result in a meaningful opportunity to reduce health risks [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xCfQfPLZ","properties":{"formattedCitation":"(USEPA, 2011a)","plainCitation":"(USEPA, 2011a)","noteIndex":0},"citationItems":[{"id":191,"uris":["http://zotero.org/groups/945096/items/4EFIN6HN"],"uri":["http://zotero.org/groups/945096/items/4EFIN6HN"],"itemData":{"id":191,"type":"webpage","title":"Drinking Water: Regulatory Determination on Perchlorate. Federal Register Notice. 76 FR No. 29. Pages 7762-7767. (February 11, 2011) (to be codified at 40 C.F.R pt. 141).","URL":"https://www.federalregister.gov/articles/2011/02/11/2011-2603/drinking-water-regulatory-determination-on-perchlorate","shortTitle":"Drinking Water: Regulatory Determination on Perchlorate. Federal Register Notice. 76 FR No. 29. Pages 7762-7767. (February 11, 2011) (to be codified at 40 C.F.R pt. 141).","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2011"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Based on the best available scientific information on the health effects of perchlorate, the EPA is proposing a maximum contaminant level goal (MCLG) of 56 micrograms per liter (µg/L). The EPA is also proposing an enforceable maximum contaminant level (MCL) of 56 µg/L and compliance monitoring requirements consistent with the Standardized Monitoring Framework for inorganic contaminants in the Title 40 Code of Federal Regulations (CFR) 141.23(c).

1.1 Purpose of Economic Analysis

The purpose of this economic analysis is to provide a description of the potential benefits and costs of the proposed perchlorate NPDWR. An economic analysis is required for all significant rules under Executive Order (EO) 12866 (*Regulatory Planning and Review*). In addition, Section 1412(b)(3)(C) of the 1996 Amendments to the Safe Drinking Water Act (SDWA) requires the EPA to prepare a Health Risk Reduction and Cost Analysis (HRRCA) in support of any NPDWR that includes an MCL. The analysis in this document addresses these and other regulatory reporting requirements. With respect to the HRRCA requirements, this document provides the following:

- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level (Chapter [REF _Ref523452255 \r \h]);
- Quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur from reductions in co-occurring contaminants that may be attributed solely to compliance with the MCL, excluding benefits resulting from compliance with other proposed or promulgated regulations (Chapter [REF _Ref523452255 \r \h]);
- Quantifiable and non-quantifiable costs for which there is a factual basis in the rulemaking record to conclude that such costs are likely to occur solely as a result of

compliance with the MCL, including monitoring, treatment, and other costs, and excluding costs resulting from compliance with other proposed or promulgated regulations (Chapter [REF _Ref525051776 \r \h]);
- Incremental costs and benefits associated with each alternative MCL considered (Chapter [REF _Ref535310132 \r \h]);
- Effects of the contaminant on the general population and on groups within the general population, such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other sub-populations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population (Chapter [REF _Ref523452255 \r \h]);
- Any increased health risk that may occur as the result of compliance, including risks associated with co-occurring contaminants (Chapter [REF _Ref523452255 \r \h]); and
- Other relevant factors, including the quality and extent of the information, the uncertainties in the analysis, and factors with respect to the degree and nature of the risk (Chapters [REF _Ref523452255 \r \h] to [REF _Ref535310160 \r \h]).

1.2 Outline

This document contains the following:

- Chapter [REF _Ref535310173 \r \h] – [REF _Ref535310189 \h] – describes the proposed NPDWR and alternatives the Agency considered;
- Chapter [REF _Ref535310292 \r \h] – [REF _Ref535310201 \h] – provides key information about current conditions that form the baseline for the subsequent benefit and cost analysis, including a description of perchlorate occurrence in drinking water and the potentially affected entities;
- Chapter [REF _Ref523452255 \r \h] – [REF _Ref523452255 \h] – provides a summary of the health effects of concern, the basis for the proposed MCLG, and the method that the Agency used to estimate the health risk reductions of proposing an enforceable MCL;
- Chapter [REF _Ref525051776 \r \h] – [REF _Ref525051776 \h] – describes the potentially affected entities and the basis for estimating costs to implement the proposed rule and comply with the MCL;
- Chapter [REF _Ref535310268 \r \h] – [REF _Ref535310229 \h] – provides side-by-side comparison of the benefits and costs by the proposed rule alternative;
- Chapter [REF _Ref535310259 \r \h] – [REF _Ref535310237 \h] – addresses several reporting requirements under various statutes and Executive Orders; and
- Appendices – provide additional details for selected topics in the main document.

Information in the chapters often summarizes more detailed technical support documents, which are cited throughout the text.

1.3 Public Health Concerns to Be Addressed

Perchlorate is an anion containing one chlorine atom bound to four oxygen atoms (ClO_4^-). It combines with cations to form salts including ammonium perchlorate and potassium perchlorate. Each salt has different chemical properties including molecular weight, density, boiling/melting

points, and solubility [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"MwgdYrvr","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Perchlorate ingestion – via drinking water or food – can adversely affect human health. The main target organ for perchlorate toxicity is the thyroid gland, where perchlorate competes with iodide for transport and, therefore, may lead to decreases in iodide uptake, which can adversely affect hormone production levels. These changes in thyroid hormones in a pregnant or nursing woman can be linked to changes in the intelligence quotient (IQ) in her offspring using dose-response functions derived from the peer-reviewed literature. Chapter 4 describes these relationships in more detail because they form the basis for a quantitative benefits analysis. Chapter 4 also identifies other adverse neurological effects and cardiovascular disease (CVD) that may be linked to perchlorate exposure.

1.3.1 Rule Objectives and Public Health Concerns

The proposed rule will reduce perchlorate concentrations in the drinking water distributed by PWSs that exceed the proposed MCL. These reductions will ultimately reduce the incidence of IQ impacts among offspring born to women exposed to high perchlorate concentrations under baseline occurrence conditions. The proposed rule also includes requirements for every affected drinking water system to conduct initial monitoring to determine whether perchlorate exceeds the proposed MCL. Customers of these systems will benefit from knowing whether they are exposed to perchlorate in excess of the MCL and, if so, what measures they can take to protect themselves and their families until the treatment or other control efforts reduce perchlorate to a compliant level.

1.3.2 Sources and Mechanisms of Exposure

The Agency's *Perchlorate Occurrence and Monitoring Report* technical support document [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"TKLDxDYY","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] provides a review of perchlorate sources, fate, and transport. The following discussion provides a brief summary of that discussion.

Perchlorate is naturally occurring and man-made. Natural sources include geologic materials such as potash ore from New Mexico and sodium nitrate-rich soils in Chile, which have been

used to produce fertilizers applied in the United States. Man-made sources include the use of ammonium perchlorate as an oxidizer in solid fuels for rockets and fireworks. Major production sites include facilities in Nevada and Utah.

Perchlorate is likely to be mobile in soil and aqueous media because perchlorate salts are highly soluble and unlikely to sorb to minerals or organic matter. Dissolved in water, the perchlorate ion is unlikely to undergo reduction, hydrolysis, or direct photolysis; form insoluble metal complexes; or volatilize from water. Therefore, perchlorate is likely to persist in water absent biological removal or uptake processes. Releases to air are likely to result in eventual deposition to soil or water. Thus, once perchlorate reaches surface or ground water sources of drinking water, these characteristics suggest it is likely to persist in the water. These same characteristics indicate that effective treatment processes include biological removal and anion exchange.

1.4 Regulatory History and Background

This section describes the process that led the Agency to propose an NPDWR for perchlorate. The SDWA requires the EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). The CCL is a list of drinking water contaminants that are known to occur in PWSs and are not currently subject to the EPA drinking water regulations. Contaminants listed on the CCL may require future regulation under the SDWA. The EPA uses the CCL to identify priority contaminants for regulatory decision-making and information collection. The EPA included perchlorate on the first, second, and third CCLs published in 1998, 2005, and 2009, respectively.

After including contaminants on the CCL, the Agency continues to collect data and encourage further research on listed contaminants to better understand potential health effects and at what levels they occur in drinking water. One avenue for collecting occurrence data for contaminants that are suspected to be present in drinking water and do not have health-based standards set under the SDWA is through the Unregulated Contaminant Monitoring Rule (UCMR). The UCMR provides for monitoring of up to 30 contaminants every 5 years at large systems and a representative sample of small PWSs serving less than or equal to 10,000 people. Analytical results are stored in a National Contaminant Occurrence Database (NCOD). The first UCMR cycle (UCMR 1) required monitoring for 26 contaminants, including perchlorate, between 2001 and 2003.

In 2005, at the request of the EPA and other federal agencies, the National Research Council (NRC) evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"PINY0WnN","properties":{"formattedCitation":"(NRC, 2005)","plainCitation":"(NRC, 2005)","noteIndex":0},"citationItems":[{"id":349,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":349,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"NRC"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}]. Based on NRC's recommendations, the EPA adopted a reference dose (RfD) of 0.7 micrograms per kilogram per day (µg/kg/day) based on a study [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a3u94lt6me","properties":{"formattedCitation":"(Greer et al., 2002)","plainCitation":"(Greer et al., 2002)","noteIndex":0},"citationItems":[{"id":387,"uris":["http://zotero.org/groups/945096/items/6AKUNIX6"],"uri":["http://zotero.org/groups/945096/items/6AKUNIX6"],"itemData":{"id":387,"type":"article-journal","title":"Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans","container-title":"Environmental Health Perspectives","page":"927","volume":"110","issue":"9","author":[{"family":"Greer","given":"Monte A."},{"family":"Goodman","given":"Gay"},{"family":"Pleus","given":"Richard C."},{"family":"Greer","given":"Susan E."}],"issued":{"date-parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] in healthy adults for the inhibition of radioactive iodide uptake and the application of an uncertainty factor of 10 for intraspecies variability [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0oHz805e","properties":{"formattedCitation":"(USEPA, 2005b)","plainCitation":"(USEPA, 2005b)","noteIndex":0},"citationItems":[{"id":1007,"uris":["http://zotero.org/groups/945096/items/LHANJBR6"],"uri":["http://zotero.org/groups/945096/items/LHANJBR6"],"itemData":{"id":1007,"type":"article","title":"Integrated Risk Information System (IRIS) Chemical Assessment Summary: Perchlorate (ClO4-) and Perchlorate Salts","publisher":"USEPA National Center for Environmental Assessment","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In October 2008, the EPA published a preliminary regulatory determination not to regulate perchlorate in drinking water using a Health Reference Level (HRL) of 15 µg/L based on the RfD of 0.7 µg/kg/day [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"FZ6WMtAv","properties":{"formattedCitation":"(USEPA, 2008a)","plainCitation":"(USEPA, 2008a)","noteIndex":0},"citationItems":[{"id":934,"uris":["http://zotero.org/groups/945096/items/HBX88QM9"],"uri":["http://zotero.org/groups/945096/items/HBX88QM9"],"itemData":{"id":934,"type":"article-journal","title":"Drinking water: Preliminary regulatory determination on perchlorate","container-title":"Federal Register","volume":"73","issue":"198","abstract":"SUMMARY: This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water Act (SDWA). The Agency has determined that a national primary drinking water regulation (NPDWR) for perchlorate would not present \"a meaningful opportunity for health risk reduction for persons served by public water systems." The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate List (CCL). EPA included perchlorate on the first and second CCLs that were published in the Federal Register on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the Federal Register on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will

make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with technical information that they may use in addressing local contamination.","ISSN":"ISSN 0097-6326 EISSN 2167-2520","shortTitle":"Federal Register","journalAbbreviation":"Fed. Reg.","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The preliminary determination found that perchlorate did not occur with a frequency and at levels of public health concern, and that development of a regulation did not present a meaningful opportunity for health risk reduction for persons served by PWSs.

In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 μg/kg/day and life stage-specific bodyweight and exposure information [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"XzGawKtq","properties":{"formattedCitation":"(USEPA, 2009a)","plainCitation":"(USEPA, 2009a)","noteIndex":0},"citationItems":[{"id":309,"uris":["http://zotero.org/groups/945096/items/ILBCYL66"],"uri":["http://zotero.org/groups/945096/items/ILBCYL66"],"itemData":{"id":309,"type":"report","title":"Inhibition of the Sodium-Iodide Symporter By Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically Based Pharmacokinetic (PBPK) Modeling (Final Report)","collection-title":"EPA/600/R-08/106A","publisher-place":"Washington, D.C.","event-place":"Washington, D.C.","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2009"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

After considering comments on the October 2008 and August 2009 notices, the EPA made a final determination in February 2011 to regulate perchlorate in drinking water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"E1I1fclP","properties":{"formattedCitation":"(USEPA, 2011a)","plainCitation":"(USEPA, 2011a)","noteIndex":0},"citationItems":[{"id":191,"uris":["http://zotero.org/groups/945096/items/4EFIN6HN"],"uri":["http://zotero.org/groups/945096/items/4EFIN6HN"],"itemData":{"id":191,"type":"webpage","title":"Drinking Water: Regulatory Determination on Perchlorate. Federal Register Notice. 76 FR No. 29. Pages 7762-7767. (February 11, 2011) (to be codified at 40 C.F.R pt. 141).","URL":"https://www.federalregister.gov/articles/2011/02/11/2011-2603/drinking-water-regulatory-determination-on-perchlorate","shortTitle":"Drinking Water: Regulatory Determination on Perchlorate. Federal Register Notice. 76 FR No. 29. Pages 7762-7767. (February 11, 2011) (to be codified at 40 C.F.R pt. 141).","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2011"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The Agency found that perchlorate may have an adverse effect on the health of persons and is known to occur in public drinking water systems with a frequency and at levels that present a public health concern. As a result of the

determination, the EPA initiated the process to develop an MCLG and NPDWR for perchlorate under the SDWA.

Since then, the EPA has developed a novel approach for deriving an MCLG for perchlorate in drinking water based on feedback from the EPA's Science Advisory Board (SAB), including the use of a biologically based dose response (BBDR) model [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"lWXxamER","properties":{"formattedCitation":"(USEPA, 2018e)","plainCitation":"(USEPA, 2018e)","noteIndex":0},"citationItems":[{"id":926,"uris":["http://zotero.org/groups/945096/items/ANBBTDKU"],"uri":["http://zotero.org/groups/945096/items/ANBBTDKU"],"itemData":{"id":926,"type":"report","title":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","shortTitle":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

1.5 Rationale for the Proposed Regulation

This section provides the statutory and economic rationales for choosing a regulatory approach to address the public health consequences of drinking water contamination.

1.5.1 Statutory Authority

Section 1412(b)(1)(A) of the SDWA requires the EPA to establish NPDWRs for contaminants that may have an adverse public health effect; that are known to occur or that present a substantial likelihood of occurring once in PWSs, at a frequency and level of public concern; and that present a meaningful opportunity for health risk reduction for persons served by PWSs.

1.5.2 Economic Rationale for Regulation

The Office of Management and Budget (OMB) Circular A-4 (1996 and 2003) states that "in order to establish the need for the proposed action, the analysis should discuss whether the problem constitutes a significant market failure." This section describes the types of market failures that NPDWRs address.

In a perfectly competitive market, market forces guide buyers and sellers to attain the best possible social outcome. A perfectly competitive market occurs when there are many producers of a product, many buyers for the product, and both producers and buyers have complete knowledge regarding the products of each firm. Also, there must not be any barriers to entry into the industry, and producers in the industry must not have any advantage over potential new producers. Several factors in the public water supply industry do not satisfy the requirements for a perfect market and lead to market failures that may require regulation.

First, water utilities are natural monopolies. A natural monopoly exists because it is not economically efficient to have multiple suppliers competing to build multiple systems of pipelines, reservoirs, wells, and other facilities. Instead, a single firm or government entity performs these functions generally under public control. Under monopoly conditions, consumers are provided only one level of service with respect to the quality of the product, in this case

drinking water quality. If consumers do not believe that the market of safety in public health production is adequate, they cannot simply switch to another water utility or a perceived higher-quality source of supply (e.g., bottled water) without incurring additional cost.

Second, high information and transaction costs impede the public's understanding of health and safety issues concerning drinking water quality. The types of health risks potentially posed by trace quantities of drinking water contaminants involve the analysis and distillation of complex toxicological data and health sciences. The EPA developed the Consumer Confidence Report (CCR) rule to make water quality information more easily available to consumers. The CCR rule requires community water systems (CWSs) to mail their customers an annual report on local drinking water quality. However, consumers still have to analyze this information for its health risk implications. Even if informed consumers are able to engage utilities regarding these health issues, the costs of such engagement, known as "transaction costs" (in this case measured in personal time and commitment), present another significant impediment to consumer expression of risk preference.

SDWA regulations are intended to provide a level of protection from exposure to drinking water contaminants that would not otherwise occur in the existing market environment of public water supply. The regulations set minimum performance requirements for all public water supplies in order to reduce the risk confronted by all consumers from exposure to drinking water contaminants. SDWA regulations are not intended to restructure market mechanisms or to establish competition in supply. Rather, SDWA standards establish the level of service to be provided in order to better reflect the public's preference for safety. The Federal regulations remove the high information and transaction costs by acting on behalf of all consumers in balancing the risk reduction and the social costs of achieving this reduction.

2 Consideration of Regulatory Alternatives

The Agency's proposed rule comprises the following elements: an MCLG, an MCL, and monitoring and reporting requirements. This section describes each element of the proposed rule and identifies the alternatives that the Agency considered during the rule-making process.

2.1 MCLG

Section 1412 (b)(4)(A) of the SDWA requires that – when regulating a contaminant – the EPA first sets an MCLG "at the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." MCLGs are non-enforceable health goals. For this rulemaking, the EPA is proposing to set an MCLG of 56 µg/L for perchlorate based on a 2 IQ point decrease. Section 4 describes the basis for this MCLG. The Agency also considered an alternative MCLG of 18 µg/L based on a 1 IQ point decrease.

2.2 MCL Alternatives

Section 1412 (b)(4)(B) of the SDWA requires that when the EPA sets an enforceable MCL, it is "as close to the maximum contaminant level goal as is feasible." Section 1412 (b)(4)(D) defines feasible as follows: "feasible with the use of the best technology, treatment techniques and other means which the Administrator finds, after examination for efficacy under field conditions and not solely under laboratory conditions, are available (taking cost into consideration)." Furthermore, Section 1401 (1)(A)(i) defines an MCL as feasible when "it is economically and technologically feasible to ascertain the level of such contaminant in water in public water systems." Finally, under Section 1412 (b)(6), the Administrator can determine that the benefits of an MCL as close as feasible to the MCLG "would not justify the costs of complying with the level" and promulgate an MCL "that maximizes health risk reduction benefits at a cost that is justified by the benefits." The EPA determined that an MCL of 56 µg/L is feasible and, therefore, is proposing to set the MCL equal to the MCLG of 56 µg/L. For the alternative MCLG of 18 µg/L, the Agency determined that setting the MCL equal to the MCLG was feasible.

The proposed rule applies to certain PWSs. A PWS is a system that provides water for human consumption to the public through pipes or other constructed conveyances and has at least 15 service connections or regularly serves at least 25 individuals for at least 60 days per year [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a15poirtvap","properties":{"formattedCitation":"(USEPA, 2017b)","plainCitation":"(USEPA, 2017b)","noteIndex":0},"citationItems":[{"id":922,"uris":["http://zotero.org/groups/945096/items/X6GF6JJW"],"uri":["http://zotero.org/groups/945096/items/X6GF6JJW"],"itemData":{"id":922,"type":"webpage","title":"Information about Public Water Systems","URL":"https://www.epa.gov/dwreginfo/information-about-public-water-systems","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2017"]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. PWSs may be publicly or privately owned. Types of PWSs include CWSs and non-community water systems (NCWSs), which may be transient or non-transient. The PWS types are defined as follows [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"BDOZjmky","properties":{"formattedCitation":"(USEPA,

2009b; 2017b)","plainCitation":"(USEPA, 2009b;
2017b)","noteIndex":0},"citationItems":[{"id":925,"uris":["http://zotero.org/groups/945096/item
s/QPD46SEA"],"uri":["http://zotero.org/groups/945096/items/QPD46SEA"],"itemData":{"id":92
5,"type":"article","title":"2006 Community Water System Survey - Volume I:
Overview","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-
survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",2]]},"accessed":{"date-
parts":[["2018",8,17]]}}},{"id":922,"uris":["http://zotero.org/groups/945096/items/X6GF6JJW"]
,"uri":["http://zotero.org/groups/945096/items/X6GF6JJW"],"itemData":{"id":922,"type":"webp
age","title":"Information about Public Water
Systems","URL":"https://www.epa.gov/dwreginfo/information-about-public-water-
systems","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2017"]]},"accessed":{"date-
parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}]:

- CWSs supply water to at least 15 service connections used by year-round residents or regularly serve at least 25 year-round residents.
- NCWSs do not serve year-round residents. These water systems serve areas where the people do not stay for long periods of time or where the same population is served less than year-round. Two categories of NCWSs are:
    - Non-transient non-community water systems (NTNCWSs) serve at least 25 of the same people for at least 6 months of the year. Examples include schools and office buildings.
    - Transient non-community water systems (TNCWSs) serve fewer than 25 of the same people over 6 months of the year. Examples include gas stations and campgrounds.

The EPA proposes to regulate perchlorate at CWSs and NTNCWSs.

2.3 Monitoring Requirements

The EPA is proposing the following monitoring requirements for perchlorate:

- Initial monitoring – one year of monitoring by all affected systems to determine compliance with the proposed MCL; and
- Long-term monitoring consistent with the Standardized Monitoring Framework for inorganic contaminants.

2.3.1 Initial Monitoring Requirements

The Agency is proposing that all CWSs and NTNCWSs conduct one year of initial monitoring. Large CWSs, which serve more than 10,000 people, will conduct initial monitoring within the first 3 years after the effective date. Small CWSs, which serve up to 10,000 people, and all NTNCWSs have 6 years after the effective date to conduct initial monitoring. To meet the initial monitoring requirement, all water systems must collect four quarterly samples.

2.3.2 Long-Term Monitoring Requirements

Following their respective initial monitoring period, CWS and NTNCWSs will conduct long-term monitoring according to the Standardized Monitoring Framework [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aGOrxjKr","properties":{"formattedCitation":"(USEPA, 2004)","plainCitation":"(USEPA, 2004)","noteIndex":0},"citationItems":[{"id":993,"uris":["http://zotero.org/groups/945096/items/XIN79HTB"],"uri":["http://zotero.org/groups/945096/items/XIN79HTB"],"itemData":{"id":993,"type":"article","title":"The Standardized Monitoring Framework: A Quick Reference Guide","publisher":"EPA-816-F-04-010","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2004"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Monitoring frequency depends on the water source and whether a system qualifies for a perchlorate monitoring waiver or exceeds the MCL. [REF _Ref525846605 \h] shows the proposed monitoring frequencies.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Long-Term Perchlorate Monitoring Requirements

Water Source	Waiver	No Waiver, Reliably and Consistently ≤ MCL	> MCL or Not Reliably and Consistently ≤ MCL
Groundwater	1 sample every 9 years	1 sample every 3 years	Quarterly samples
Surface water	1 sample every 9 years	Annual sample	Quarterly samples

Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"IJ22Yulq","properties":{"formattedCitation":"(2004)","plainCitation":"(2004)","noteIndex":0},"citationItems":[{"id":993,"uris":["http://zotero.org/groups/945096/items/XIN79HTB"],"uri":["http://zotero.org/groups/945096/items/XIN79HTB"],"itemData":{"id":993,"type":"article","title":"The Standardized Monitoring Framework: A Quick Reference Guide","publisher":"EPA-816-F-04-010","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2004"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

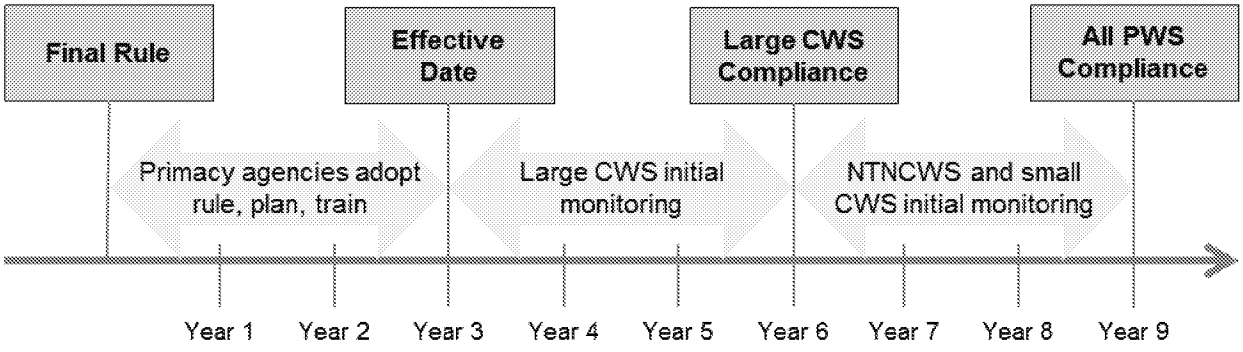
2.4 Reporting Requirements

The proposed rule includes several reporting requirements. Water systems must provide monitoring results to primacy agencies. These agencies must report violation-related information to the EPA. Systems may also include perchlorate monitoring information in their annual CCR. Finally, systems will have public notification requirements in the event of an MCL violation.

2.5 Implementation Schedule

The EPA is proposing effective dates that vary by system size and type. [REF _Ref529978990 \h] provides an overview of the implementation schedule. The effective date of the rule is three years after the rule finalization. Then, large CWSs will have three years (i.e. the first compliance period after the effective date) to complete their initial monitoring and install needed controls. NTNCWSs and small CWSs will complete their initial monitoring in the subsequent 3-year compliance period (i.e., years six to nine). All covered systems will be in compliance by year nine.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Proposed Rule Timeline



2.6 Summary of Regulatory Alternatives

[REF _Ref525846788 \h] provides a summary of the regulatory alternatives that EPA considered for the proposed perchlorate rule.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Long-Term Perchlorate Monitoring Requirements

Element	Proposed Rule – Preferred Alternative	Alternative A
MCLG	56 µg/L	18 µg/L
MCL	56 µg/L	18 µg/L
Monitoring	Standard Monitoring Framework	Standard Monitoring Framework

3 Baseline Analysis

3.1 Introduction

This chapter presents the data and assumptions used to establish the baseline for calculating the costs, benefits, and economic impacts of the proposed perchlorate rule. The baseline is the EPA's expectation of the conditions that would exist in the absence of perchlorate regulation. The baseline includes a profile of the PWSs that are potentially affected by a perchlorate regulation and current demographic information to characterize the exposed population. The baseline also includes estimates of perchlorate occurrence and exposure, which affect the Agency's analysis of costs and benefits of the proposed rule.

3.1.1 Background and Purpose

The purpose of the baseline analysis is to describe the data available to develop baseline characterization of the water supply industry, prior to the promulgation and implementation of an NPDWR for perchlorate. In the baseline analysis, the EPA defines the various types of water systems and provides information on the number and size of these water systems. The EPA also presents characteristics of the water systems, including population served, number of entry points, current treatment technologies that are in place, and the amount of production. The baseline analysis also discusses water consumption per household, estimates of current perchlorate occurrence, and population groups that may be susceptible to the health effects of perchlorate exposure.

3.1.2 Chapter Organization

The remainder of this chapter is organized into three sections. Section [REF _Ref523471222 \r \h] provides a description of the data sources used in the baseline analysis. Section [REF _Ref523415085 \r \h] characterizes the water supply industry as outlined above; this section also includes assumptions made in the analysis. The EPA then discusses current perchlorate occurrence in Section [REF _Ref523404705 \r \h], and sensitive life stages and other populations in Section [REF _Ref523459825 \r \h].

3.2 Data Sources

Data sources for the baseline analysis include data specific to the water supply industry and other information needed to characterize baseline conditions. Specifically, the EPA characterizes water systems using the EPA's Safe Drinking Water Information System (SDWIS) database and the 2006 Community Water System Survey (CWSS). The Agency uses perchlorate monitoring data from the UCMR 1 and comparable, but more recent, data sources to characterize baseline exposure to perchlorate in drinking water. The data sources are described in detail below.

3.2.1 SDWIS/FED and Other Sources for Water System Data

The EPA uses the SDWIS Fed Data Warehouse (SDWIS/FED) to characterize the universe of affected systems. SDWIS/FED contains information on the more than 146,000 active PWSs in the United States, as reported by states and the EPA Regions [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"QA4gnxdO","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA,

2018f)","noteIndex":0},"citationItems":[{"id":923,"uris":["http://zotero.org/groups/945096/items/CW34PNAZ"],"uri":["http://zotero.org/groups/945096/items/CW34PNAZ"],"itemData":{"id":923,"type":"article","title":"Safe Drinking Water Information System Federal Reports Search","URL":"https://ofmpub.epa.gov/apex/sfdw/f?p=108:200::::::","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]},"accessed":{"date-parts":[["2018",8,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Information reported includes basic information on each water system, details on each PWS's compliance and violation history, and states' actions to enforce drinking water regulations [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"PNHTPwkH","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":923,"uris":["http://zotero.org/groups/945096/items/CW34PNAZ"],"uri":["http://zotero.org/groups/945096/items/CW34PNAZ"],"itemData":{"id":923,"type":"article","title":"Safe Drinking Water Information System Federal Reports Search","URL":"https://ofmpub.epa.gov/apex/sfdw/f?p=108:200::::::","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]},"accessed":{"date-parts":[["2018",8,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Basic information about PWSs includes location, number of people served, system type (e.g., CWS or NTNCWS), operation schedule (year-round or seasonal), ownership type (public or private), and characteristics of the source water. To characterize baseline conditions for this analysis, the EPA downloaded data from SDWIS/FED in August 2018.[1]

Another data source specific to the water supply industry is the 2006 CWSS report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"kFw5Lm0h","properties":{"formattedCitation":"(USEPA, 2009b)","plainCitation":"(USEPA, 2009b)","noteIndex":0},"citationItems":[{"id":925,"uris":["http://zotero.org/groups/945096/items/QPD46SEA"],"uri":["http://zotero.org/groups/945096/items/QPD46SEA"],"itemData":{"id":925,"type":"article","title":"2006 Community Water System Survey - Volume I: Overview","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",2]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This survey has been administered periodically since 1976 and the most recent version is the 2006 CWSS. In the survey, the EPA collected information on major operational and financial characteristics of CWSs. CWSs are PWSs that have at least 15 service connections used year-round or regularly serve at least 25 people year-round [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a28flh1e4jm","properties":{"formattedCitation":"(USEPA, 2009b)","plainCitation":"(USEPA, 2009b)","noteIndex":0},"citationItems":[{"id":925,"uris":["http://zotero.org/groups/945096/items/QPD46SEA"],"uri":["http://zotero.org/groups/945096/items/QPD46SEA"],"itemData":{"id":925,"type":"article","title":"2006 Community Water System Survey - Volume I: Overview","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-

[1] [HYPERLINK "https://ofmpub.epa.gov/apex/sfdw/f?p=108:1:::NO:1"], data extracted August 14, 2018.

survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",2]]},"accessed":{"date-parts":[["2018",8,17]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

3.2.2 Other Data and Information Used

The EPA's *Perchlorate Occurrence and Monitoring Report* is the source for national perchlorate occurrence data [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"uKDF3cH2","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This document describes the available data and analytical approaches that the EPA used to assess the baseline perchlorate occurrence in CWSs and NTNCWSs. The document also provides detailed estimates of perchlorate occurrence in drinking water.

Additional data and information used in analyzing the baseline conditions include data on the number of people in population groups that may be particularly susceptible to the health effects of perchlorate exposure. These data include U.S. Census Bureau population data and the National Center for Health Statistics annual live birth rates.

3.3 Baseline Profile

The proposed rule for perchlorate will apply to CWSs and NTNCWSs, and will not affect TNCWSs. Key characteristics of the affected systems are their service population size, type, ownership, and source water. This section provides details on these systems grouped by these characteristics.

3.3.1 Number and Size of PWSs

The proposed rule will affect CWSs and NTNCWSs. The EPA uses a SDWIS data extract from August 2018 to determine the number of these water systems in the United States by system size category, source water, ownership, and system type. Both CWSs and NTNCWSs have more groundwater sources than surface water sources ([REF _Ref523343598 \h]). CWSs make up approximately three-fourths (49,879 out of 67,497) of regulated water systems. NTNCWSs are more likely to be privately owned than CWSs ([REF _Ref523343749 \h]) and be a small system ([REF _Ref523343805 \h]). The exhibits show national totals and revised national totals that exclude systems in California and Massachusetts, which are the subset of regulated systems that would incur costs and benefits under the proposed rule. As noted in Section [REF _Ref523347586 \r \h * MERGEFORMAT], California and Massachusetts regulations supersede the proposed MCL. The systems in these states must comply with MCLs that are less than the proposed MCL or alternative MCL. Therefore, the EPA assumed that the proposed rule would not impose any incremental compliance costs on these systems.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Distribution of Affected Systems by Water Source and System Type

Water Source	CWSs (including CA and MA)	NTNCWSs (including CA and MA)	Total Systems (including CA and MA)	CWSs (excluding CA and MA)	NTNCWSs (excluding CA and MA)	Total Systems (excluding CA and MA)
Groundwater	38,202	16,860	55,062	35,568	15,220	50,788
Surface water	11,677	758	12,435	10,634	654	11,288
Total	49,879	17,618	67,497	46,202	15,874	62,076

Source: SDWIS/FED 2018 data extract [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"FXSyRdlI","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":923,"uris":["http://zotero.org/groups/945096/items/CW34PNAZ"],"uri":["http://zotero.org/groups/945096/items/CW34PNAZ"],"itemData":{"id":923,"type":"article","title":"Safe Drinking Water Information System Federal Reports Search","URL":"https://ofmpub.epa.gov/apex/sfdw/f?p=108:200::::::","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]},"accessed":{"date-parts":[["2018",8,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Distribution of Affected Systems by Ownership and System Type

Ownership	CWSs (including CA and MA)	NTNCWSs (including CA and MA)	Total Systems (including CA and MA)	CWSs (excluding CA and MA)	NTNCWSs (excluding CA and MA)	Total Systems (excluding CA and MA)
Private	22,865	12,266	35,131	20,742	11,153	31,895
Public/other	27,014	5,352	32,366	25,460	4,721	30,181
Total	49,879	17,618	67,497	46,202	15,874	62,076

Source: SDWIS/FED 2018 data extract [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"gsHmnekE","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":923,"uris":["http://zotero.org/groups/945096/items/CW34PNAZ"],"uri":["http://zotero.org/groups/945096/items/CW34PNAZ"],"itemData":{"id":923,"type":"article","title":"Safe Drinking Water Information System Federal Reports Search","URL":"https://ofmpub.epa.gov/apex/sfdw/f?p=108:200::::::","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]},"accessed":{"date-parts":[["2018",8,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Distribution of Affected Systems by Size and System Type

Service Population	CWSs (including CA and MA)	NTNCWSs (including CA and MA)	Total Systems (including CA and MA)	CWSs (excluding CA and MA)	NTNCWSs (excluding CA and MA)	Total Systems (excluding CA and MA)
Small (≤ 10,000)	45,553	17,585	63,138	42,481	15,844	58,325
Large (> 10,000)	4,326	33	4,359	3,721	30	3,751
Total	49,879	17,618	67,497	46,202	15,874	62,076

Source: SDWIS/FED 2018 data extract [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ofFRpGY2","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":923,"uris":["http://zotero.org/groups/945096/items/CW34PNAZ"],"uri":["http://zotero.org/groups/945096/items/CW34PNAZ"],"itemData":{"id":923,"type":"article","title":"Safe Drinking Water Information System Federal Reports Search","URL":"https://ofmpub.epa.gov/apex/sfdw/f?p=108:200::::::","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]},"accessed":{"date-parts":[["2018",8,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

3.3.2 System Size and Population Served

SDWIS/FED also provides information on the retail population served by each system. Baseline health risks are a function of service populations. National population served estimates can also be disaggregated by source water ([REF _Ref523344075 \h]), system type ([REF _Ref523344088 \h]), and system size category ([REF _Ref523344097 \h]).[2] CWS service populations are substantially larger than NTNCWS service populations. Among CWSs, publicly owned systems and large systems account for a large majority of the total population served. The exhibits include total national estimates as well as national estimates excluding the service populations of systems in California and Massachusetts. Systems in these states must meet state MCLs that are lower than the proposed MCL, so there will be no perchlorate reductions associated with the proposed rule and, therefore, no benefits.

[2] The populations across CWSs and NTNCWSs are not additive because the population served by an NTNCWS can also be served by a CWS. For example, students at a school that is served by an NTNCWS may also consume water provided by a CWS at home.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Aggregate Service Population by Water Source and System Type

Water Source[a]	CWSs (including CA and MA)	NTNCWSs (including CA and MA)	CWSs (excluding CA and MA)	NTNCWSs (excluding CA and MA)
Groundwater	89,232,288	5,216,951	80,367,122	4,804,167
Surface water	219,408,388	1,289,825	176,786,648	1,175,137
Total	308,640,676	6,506,776	257,153,770	5,979,304

Source: SDWIS/FED 2018 data extract [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"4FPuHD93","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":923,"uris":["http://zotero.org/groups/945096/items/CW34PNAZ"],"uri":["http://zotero.org/groups/945096/items/CW34PNAZ"],"itemData":{"id":923,"type":"article","title":"Safe Drinking Water Information System Federal Reports Search","URL":"https://ofmpub.epa.gov/apex/sfdw/f?p=108:200::::::","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]},"accessed":{"date-parts":[["2018",8,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

a. Forty-four systems serving 41,316 people (24 systems serving 37,635 people in included states) have unspecified source water; for the purpose of this analysis, the EPA assumed that these systems use groundwater.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Aggregate Service Population by Ownership and System Type

Ownership	CWSs (including CA and MA)	NTNCWSs (including CA and MA)	CWSs (excluding CA and MA)	NTNCWSs (excluding CA and MA)
Private	36,740,435	3,481,164	29,240,150	3,286,132
Public	271,900,241	3,025,612	227,913,620	2,693,172
Total	308,640,676	6,506,776	257,153,770	5,979,304

Source: SDWIS/FED 2018 data extract [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CyEAJ7uL","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":923,"uris":["http://zotero.org/groups/945096/items/CW34PNAZ"],"uri":["http://zotero.org/groups/945096/items/CW34PNAZ"],"itemData":{"id":923,"type":"article","title":"Safe Drinking Water Information System Federal Reports Search","URL":"https://ofmpub.epa.gov/apex/sfdw/f?p=108:200::::::","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]},"accessed":{"date-parts":[["2018",8,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"I4ASsYq1","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Aggregate Service Population by Size and System Type

Service Population	CWSs (including CA and MA)	NTNCWSs (including CA and MA)	CWSs (excluding CA and MA)	NTNCWSs (excluding CA and MA)
Small (≤ 10,000)	53,121,502	5,573,773	53,121,502	5,573,773
Large (> 10,000)	255,519,174	933,003	204,032,268	405,531
Total	308,640,676	6,506,776	257,153,770	5,979,304

Source: SDWIS/FED 2018 data extract [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"qBR3UBpF","properties":{"formattedCitation":"(USEPA, 2018f)","plainCitation":"(USEPA, 2018f)","noteIndex":0},"citationItems":[{"id":923,"uris":["http://zotero.org/groups/945096/items/CW34PNAZ"],"uri":["http://zotero.org/groups/945096/items/CW34PNAZ"],"itemData":{"id":923,"type":"article","title":"Safe Drinking Water Information System Federal Reports Search","URL":"https://ofmpub.epa.gov/apex/sfdw/f?p=108:200::::::","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]},"accessed":{"date-parts":[["2018",8,28]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The EPA did not incorporate population growth factors in the benefit and cost analysis. Although the overall national population will tend to grow over time, the Agency does not assume that the same growth rate applies individually to each CWS and NTNCWS affected by the rule, in particular those systems that need to implement treatment changes to meet the proposed MCL. Some systems may actually be experiencing population declines. Therefore, the analysis of benefits and costs will be based on current population estimates.

3.3.3 Consumption per Household

The Agency's analysis of distributional impacts include per-household cost estimates based on the assumption that systems pass along their incremental compliance costs through customer utility bills. Although systems use a variety of approaches to billing for water costs, the EPA assumed that the incremental costs would be billed at a constant dollar-per-thousand gallons. The incremental cost per household varies with the annual consumption rate. The 2006 CWSS report provides estimates of water consumption per residential connection. In Section 7, the EPA uses data from the 2006 CWSS report to describe water consumption per residential connection by system size category and ownership type.

3.3.4 Production Profile

As noted above, the SDWIS/FED data contain estimates of service population. Treatment costs, however, are based on the volume of water treated per day, expressed as either design flow (a maximum daily treatment capacity) or average flow (the average daily production rate). The EPA uses equations to translate population served (*pop*) into design flow and average flow estimates [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mBK5bZJh","properties":{"formattedCitation":"(USEPA, 2000)","plainCitation":"(USEPA,

$$Average\ Flow = a_A(pop)^{b_A} \qquad ([\ SEQ\ Eq.\ \backslash * ARABIC\ ])$$

$$Design\ Flow = a_D(pop)^{b_D} \qquad ([\ SEQ\ Eq.\ \backslash * ARABIC\ ])$$

2000)","noteIndex":0},"citationItems":[{"id":153,"uris":["http://zotero.org/groups/945096/items/DL7WBKI6"],"uri":["http://zotero.org/groups/945096/items/DL7WBKI6"],"itemData":{"id":153,"type":"article","title":"Geometries and Characteristics of Public Water Systems","publisher":"EPA 815-R-00-024","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2000"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The functional forms of the flow equations (measuring flow in thousands of gallons per day) are as follows:

Parameters a_A, b_A, a_D, and b_D are estimated regression function coefficients that define the relationship between the population served by the water system and flow. The point values for the parameters in the flow equations vary by source water ([REF _Ref523346497 \h]). For the design flow, the EPA selected the maximum of either Equation 2 or two times the calculated average flow.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Flow Parameters by Water Source

Water Source	a_A	b_A	a_D	b_D
Groundwater	0.08575	1.05839	0.54992	0.95538
Surface water	0.14004	0.99703	0.59028	0.94573

Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mSrMObeA","properties":{"formattedCitation":"(2000)","plainCitation":"(2000)","noteIndex":0},"citationItems":[{"id":153,"uris":["http://zotero.org/groups/945096/items/DL7WBKI6"],"uri":["http://zotero.org/groups/945096/items/DL7WBKI6"],"itemData":{"id":153,"type":"article","title":"Geometries and Characteristics of Public Water Systems","publisher":"EPA 815-R-00-024","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2000"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

3.4 Occurrence of Perchlorate

EPA's *Perchlorate Occurrence and Monitoring Report* provides estimates of the baseline perchlorate occurrence in PWSs [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"qUTie4VE","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. After reviewing the available data on perchlorate in drinking water, the EPA determined that the best nationally representative source is data from the UCMR 1.

This section summarizes the EPA's perchlorate occurrence analysis [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UCKVzf9d","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Section [REF _Ref523347586 \r \h] provides an overview of UCMR 1 and its perchlorate occurrence data, Section [REF _Ref523347601 \r \h] summarizes the EPA's analysis of the UMCR 1 data, and Section [REF _Ref523347648 \r \h] summarizes the national perchlorate occurrence estimates used in the cost and benefit analyses.

3.4.1 Overview of UCMR 1 Data

The UCMR is a national drinking water monitoring program administered by the EPA. The UCMR 1 monitoring cycle included a census of all large CWSs and NTNCWSs (i.e., those serving more than 10,000 people), and a statistical sample of 800 small CWSs and NTNCWSs (i.e., those serving 10,000 people or fewer) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"sOBUvFhD","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The UMCR1 cycle was from 2001 to 2005, and most of the data collection occurred between 2001 and 2003.

The UCMR 1 data comprise perchlorate monitoring samples from systems in all 50 states, the District of Columbia, the Tribal Nations, and 4 U.S. territories (Puerto Rico, Virgin Islands, Guam, and the Northern Mariana Islands). Response rates were high: 99.6 percent of small systems and 99.0 percent of large systems provided data [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"45nk8Bn9","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Systems collected samples at each entry point to their customer distribution system.[3] Entry points are the point of compliance for the proposed rule and systems can have multiple entry points.

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[3] In response to comments on UCMR 1 data quality [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"6awaaIIF","properties":{"formattedCitation":"(U.S. Chamber of Commerce, 2012)","plainCitation":"(U.S. Chamber of Commerce, 2012)","noteIndex":3},"citationItems":[{"id":152,"uris":["http://zotero.org/groups/945096/items/CMDYPKE9"],"uri":["http://zotero.org/groups/945096/items/CMDYPKE9"],"itemData":{"id":152,"type":"article","title":"Information Quality Guidelines (IQG) Request for Correction","publisher":"Letter to USEPA. September.","author":[{"family":"U.S. Chamber of Commerce","given":""}],"issued":{"date-parts":[["2012"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the EPA reviewed the UCMR 1 data to identify instances where source water monitoring samples were accompanied by corresponding "downstream" entry point monitoring samples. In these instances, only the entry point samples provide the perchlorate concentration in water delivered to customers. Therefore, the 2013 version of the UCMR 1 dataset excludes these types of source water samples [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"88kDnU3n","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":3},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-

The sampling frequency varied by source water: four quarterly samples in a one-year period for surface water systems, and two samples at least six months apart for groundwater systems [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8NSuLNK0","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The minimum reporting level (MRL) was 4 µg/L [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"k4YEKduX","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The summary statistics in [REF _Ref523358120 \h] show total samples, entry points, and systems in the UCMR 1 perchlorate dataset. It also shows the number of reported perchlorate detections (≥ 4 µg/L) along with the corresponding number of entry points and systems reporting those results.

***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: UCMR 1 Data Summary Statistics

Item	Small System Sample[a]	Large System Census	Total
Total samples	3,295	30,837	34,132
➢ Measurements ≥ 4 µg/L	15	525	540
Total entry points	1,454	13,482	14,936
➢ Measurements ≥ 4 µg/L	8	328	336
Total systems	797	3,068	3,865
➢ Measurements ≥ 4 µg/L	8	141	149

Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UdoRmqu2","properties":{"formattedCitation":"(2018d)","plainCitation":"(2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

a. The small system values shown are sample results that have not been extrapolated to national estimates.

[REF _Ref523358221 \h] shows the populations that correspond with the occurrence summary in [REF _Ref523358120 \h]. The entry point population estimates reflect the assumption that system population is uniformly distributed across entry points (e.g., the entry point population for a system with two entry points is one-half the total system population).

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: UCMR 1 Data Service Population Summary Statistics

Item	Small System Sample[a]	Large System Census	Total
Total entry point population	2,760,570	222,853,101	225,613,671
➢ Measurements ≥ 4 µg/L	9,484	4,281,937	4,291,420
Total system population	2,760,570	222,853,101	225,613,671
➢ Measurements ≥4 µg/L	13,483	16,159,082	16,172,565

Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"LtcBtcnO","properties":{"formattedCitation":"(2018d)","plainCitation":"(2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

a. The small system values shown are sample results that have not been extrapolated to national estimates.

Because the UCMR 1 data are well over a decade old, the EPA considered potential sources of uncertainty because of changes between current conditions and conditions at the time of data collection. One important change is the adoption of perchlorate drinking water limits in two states: Massachusetts adopted a drinking water standard for perchlorate of 2 µg/L in 2006 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8DPpSrv3","properties":{"formattedCitation":"(Masschusetts Department of Environmental Protection (MassDEP), 2006)","plainCitation":"(Masschusetts Department of

Environmental Protection (MassDEP), 2006)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":151,"uris":["http://zotero.org/groups/945096/items/9893MBZH"],"uri":["http://zotero.org/groups/945096/items/9893MBZH"],"itemData":{"id":151,"type":"personal_communication","title":"Letter to Public Water Suppliers concerning new perchlorate regulations","URL":"https://www.mass.gov/lists/perchlorate-background-information-and-standards#perchlorate---final-standards-","author":[{"literal":"Massachusetts Department of Environmental Protection (MassDEP)"}],"issued":{"date-parts":[["2006"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and California promulgated a drinking water standard of 6 µg/L in 2007 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cfr6HNhg","properties":{"formattedCitation":"(California Department of Public Health, 2007)","plainCitation":"(California Department of Public Health, 2007)","noteIndex":0},"citationItems":[{"id":150,"uris":["http://zotero.org/groups/945096/items/RA45NKLQ"],"uri":["http://zotero.org/groups/945096/items/RA45NKLQ"],"itemData":{"id":150,"type":"personal_communication","title":"State Adoption of a Perchlorate Standard","URL":"https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/perchlorate/AdoptionMemotoWaterSystems-10-2007.pdf","author":[{"literal":"California Department of Public Health"}],"issued":{"date-parts":[["2007"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Systems in these states cannot exceed these limits, which are lower than the proposed federal MCL and alternative MCL. Therefore, any exceedances in the UCMR 1 data in these states overstate baseline occurrence and exposure under current conditions.

For the purpose of estimating the costs and benefits of the proposed rule, the EPA assumed that systems in California and Massachusetts comply with baseline perchlorate MCLs. Therefore, these systems will not incur incremental control costs to comply with the proposed rule. [REF _Ref525889374 \h] summarizes the UCMR 1 data pursuant to this assumption, including information about sample measurements exceeding 18 µg/L and 56 µg/L.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: UCMR 1 Data Summary Statistics, Excluding California and Massachusetts

Item	Small System Sample[a]	Large System Census	Total
Total samples	2,984	21,128	24,112
➢ Measurements ≥ 4 µg/L	13	206	219
➢ Measurements ≥ 18 µg/L	1	16	17
➢ Measurements ≥ 56 µg/L	0	2	2
Total entry points	1,327	9,118	10,445
➢ Measurements ≥ 4 µg/L	7	159	166
➢ Measurements ≥ 18 µg/L	1	16	17
➢ Measurements ≥ 56 µg/L	0	2	2
Total systems	737	2,591	3,328
➢ Measurements ≥ 4 µg/L	7	91	98
➢ Measurements ≥ 18 µg/L	1	14	15
➢ Measurements ≥ 56 µg/L	0	2	2
Total entry point population	2,537,888	183,525,431	186,063,319
➢ Measurements ≥ 4 µg/L	5,430	2,380,918	2,386,348
➢ Measurements ≥ 18 µg/L	2,155	618,406	620,561
➢ Measurements ≥ 56 µg/L	0	32,432	32,432
Total system population	2,537,888	183,525,431	186,063,319
➢ Measurements ≥ 4 µg/L	9,429	7,762,593	7,772,022
➢ Measurements ≥ 18 µg/L	4,309	696,871	701,180
➢ Measurements ≥ 56 µg/L	0	64,733	64,733

Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"wyoUjFTz","properties":{"formattedCitation":"(2018d)","plainCitation":"(2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

a. The values shown are sample results that have not been extrapolated to national estimates.

The age of the UCMR 1 data introduces additional sources of uncertainty. One is the effect of remediation efforts to reduce the sources of perchlorate in drinking water. The *Perchlorate Occurrence and Monitoring Report* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NaOQHInh","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] describes remediation efforts that have effectively reduced perchlorate levels in the Colorado River water from a range of 4 µg/L to 9 µg/L during the UCMR 1 data collection period to 1 µg/L to 2 µg/L after 2009. Systems that use the Colorado River as a water source may have lower concentrations at entry points than the values reported in the UCMR 1. Another type of change that has an uncertain impact on occurrence is the change in the universe of systems over time. Some systems operating during

the UCMR 1 data collection period are now inactive. There are also new systems that were not operating during the UCMR 1 period. Such changes over time have an uncertain impact on perchlorate occurrence and exposure.

3.4.2 Summary of the EPA's Analysis of UCMR 1 Data

The analytical approach that the EPA used to estimate perchlorate occurrence and exposure is the approach that it used to evaluate the national contaminant occurrence analyses for the six-year reviews of NPDWRs [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xqeVN1Mh","properties":{"formattedCitation":"(USEPA, 2003b)","plainCitation":"(USEPA, 2003b)","noteIndex":0},"citationItems":[{"id":1012,"uris":["http://zotero.org/groups/945096/items/775HKG64"],"uri":["http://zotero.org/groups/945096/items/775HKG64"],"itemData":{"id":1012,"type":"article","title":"Occurrence Estimation Methodology and Occurrence Findings Report for the Six-Year Review of Existing National Primary Drinking Water Regulations","URL":"https://www.epa.gov/sites/production/files/2014-12/documents/815r03006.pdf","note":"EPA-815-R-03-006","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2003",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the UCMR 1 data [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"QNSihtwR","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA, 2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and prior regulatory determinations [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"fGy4pkzB","properties":{"formattedCitation":"(USEPA, 2003a; 2008a)","plainCitation":"(USEPA, 2003a; 2008a)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1004,"uris":["http://zotero.org/groups/945096/items/WAS6UYUI"],"uri":["http://zotero.org/groups/945096/items/WAS6UYUI"],"itemData":{"id":1004,"type":"article","title":"Announcement of Regulatory Determinations for Priority Contaminants on the Drinking Water Contaminant Candidate List","publisher":"68 FR 138","shortTitle":"Federal Register","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2003"]]}}},{"id":934,"uris":["http://zotero.org/groups/945096/items/HBX88QM9"],"uri":["http://zotero.org/groups/945096/items/HBX88QM9"],"itemData":{"id":934,"type":"article-journal","title":"Drinking water: Preliminary regulatory determination on perchlorate","container-title":"Federal Register","volume":"73","issue":"198","abstract":"SUMMARY: This action presents EPA's preliminary regulatory determination for perchlorate in accordance with the Safe Drinking Water Act (SDWA). The Agency has determined that a national primary drinking water regulation (NPDWR) for perchlorate would not present \"a meaningful opportunity for health risk reduction for persons served by public water systems.\" The SDWA requires EPA to make determinations every five years of whether to regulate at least five contaminants on the Contaminant Candidate

List (CCL). EPA included perchlorate on the first and second CCLs that were published in the Federal Register on March 2, 1998 and February 24, 2005. Most recently, EPA presented final regulatory determinations regarding 11 contaminants on the second CCL in a notice published in the Federal Register on July 30, 2008. In today's action, EPA presents supporting rationale and requests public comment on its preliminary regulatory determination for perchlorate. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice. EPA plans to publish a health advisory for perchlorate at the time the Agency publishes its final regulatory determination to provide State and local public health officials with technical information that they may use in addressing local contamination.","ISSN":"ISSN 0097-6326 EISSN 2167-2520","shortTitle":"Federal Register","journalAbbreviation":"Fed. Reg.","language":"English","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. In each case, the data analysis process and presentation were peer-reviewed and subject to public and stakeholder review and comment. The approach relevant for the proposed perchlorate MCL and alternative MCL is the "Stage 1" analysis, for which an exceedance occurs if a single sample concentration is greater than a threshold such as the MCL.

EPA conducted the Stage 1 analysis at the entry-point level to derive estimates of benefits and costs that reflect the fact that a system may not have exceedances at all entry points and, therefore, benefits and costs should reflect a population smaller than the total system population.

3.4.3 Summary of National Perchlorate Occurrence

The EPA estimated Stage 1 occurrence for the proposed MCL of 56 µg/L and the alternative MCL of 18 µg/L. The results in [REF _Ref523449433 \h] and [REF _Ref523448716 \h] show the number of entry points and systems at which the highest perchlorate concentration exceeds these respective values, along with corresponding entry point service populations. Regardless of the threshold, there are exceedances at relatively few entry points or systems.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Expected Stage 1 Perchlorate Occurrence Greater than 56 µg/L

Affected Entity	Small Systems	Large Systems	Total Systems
Entry points	0	2	2
Population served	0	32,432	32,432
Water systems	0	2	2
Population served	0	64,733	64,733

Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"JZbvtgrP","properties":{"formattedCitation":"(2018d)","plainCitation":"(2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Expected Stage 1 Perchlorate Occurrence Greater than 18 µg/L

Affected Entity	Small Systems[a]	Large Systems	Total Systems
Entry points	1	16	17
Population served	2,155	605,485	607,640
Water systems	1	14	15
Population served	4,309	696,871	701,180

Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0tmWzc6h","properties":{"formattedCitation":"(2018d)","plainCitation":"(2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

a. These estimates reflect the sample data. The EPA also applied the statistical sampling weights to the results to extrapolate them to national results. The entry point at which a measurement exceeds 18 µg/L is 1 of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the 6 UCMR 1 systems in the stratum. Overall, the stratum population served accounts for 1.32% of the national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers may be exposed to perchlorate greater than 18 µg/L.

3.4.4 Number of Entry Points

The point of compliance for the proposed perchlorate MCL is the entry point to the distribution system, which can have one or more entry points. The number of entry points for CWSs are identified in the occurrence data. For systems that are not included in the occurrence data, the EPA assigned the number of entry points based on the population size classification of the system, calculated from the occurrence data. [REF _Ref524939687 \h] summarizes the number of entry points by source and population served, based on the occurrence data.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Average Number of Entry Points per PWS Based on Population Served

Size Category	Maximum Population	Number of PWSs		Number of Entry Points per PWS	
		Occurrence Data	Total	Groundwater	Surface Water
Very small	500	163	38,411	1.2	1.1
Small	3,300	290	15,104	1.8	1.0
Medium	10,000	344	4,810	2.7	1.2
Large	1,000,000	2,369	3,734	4.6	2.1
Very large	8,271,000	699	17	14.7	5.5

Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"XcGVSxov","properties":{"formattedCitation":"(2018d)","plainCitation":"(2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

3.5 Sensitive Life Stages and Other Subpopulations

According to the 1996 Amendments to the SDWA, sensitive populations include "infants, children, pregnant women, the elderly, individuals with a history of serious illness, and other subpopulations" that may have a greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population [SDWA Section 1458 (a)(1)]. In 2005, the EPA finalized guidance to differentiate health risk across life stages associated with development and growth (e.g., childhood age groups, pregnancy, and nursing) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZWU3ZKsJ","properties":{"formattedCitation":"(USEPA, 2005a)","plainCitation":"(USEPA, 2005a)","noteIndex":0},"citationItems":[{"id":149,"uris":["http://zotero.org/groups/945096/items/YKZTCBGM"],"uri":["http://zotero.org/groups/945096/items/YKZTCBGM"],"itemData":{"id":149,"type":"article","title":"Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants","publisher":"EPA/630/P-03/003F","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. In this analysis, the EPA refers to subpopulations (as defined by the SDWA) that are associated with development and growth as life stages in recognition that all humans were once occupants of early developmental life stages. Chapter [REF _Ref523452255 \r \h] identifies the sensitive life stages with respect to perchlorate ingestion. In addition, subpopulations are susceptible to perchlorate health effects due to low iodine intake and other diseases or conditions. These subpopulations include people with thyroid diseases and those with high levels of thiocyanate ingestion. There are approximately 20 million Americans with thyroid diseases [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Z1WQPRxB","properties":{"formattedCitation":"(American Thyroid Association, undated)","plainCitation":"(American Thyroid Association, undated)","noteIndex":0},"citationItems":[{"id":148,"uris":["http://zotero.org/groups/945096/items/U683NFTS"],"uri":["http://zotero.org/groups/945096/items/U683NFTS"],"itemData":{"id":148,"type":"post-weblog","title":"General Information/Press Room","URL":"https://www.thyroid.org/media-main/press-room/","author":[{"family":"American Thyroid Association","given":""}],"issued":{"literal":"undated"}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

4 Health Effects and Benefits Analysis

This chapter describes the quantifiable benefits of regulating perchlorate in drinking water, which mainly arise from reduced adverse health impacts. An overview of health effects associated with exposure to perchlorate is presented (Section [REF _Ref523327567 \n \h]), which is followed by a presentation of the approach and results for quantifying the impact of reduced perchlorate exposure from drinking water based on the subsequent reduction in lost IQ points (Section [REF _Ref523327605 \n \h]). Next, a brief discussion of additional potential benefits from reducing perchlorate exposure from drinking water that could not be quantified at this time is discussed (Section [REF _Ref523397403 \n \h]). Because many of the potential health effects of perchlorate exposure cannot be accurately quantified, the estimated benefits associated only with avoidance of lost IQ are likely an underestimate of the total benefits of a reduction of perchlorate in drinking water.

4.1 Overview of the Health Effects of Perchlorate Exposure

The main target organ for perchlorate's toxicity is the thyroid gland. Specifically, perchlorate competes with iodide[4] for transport through the sodium-iodide symporter (NIS) into the thyroid gland. Transporting iodide into the thyroid gland is a necessary step in the production of thyroid hormones triiodothyronine (T3) and thyroxine (T4) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CNjLrLOp","properties":{"formattedCitation":"(NRC, 2005)","plainCitation":"(NRC, 2005)","noteIndex":0},"citationItems":[{"id":349,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":349,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"NRC"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Therefore, perchlorate may lead to decreases in levels of these hormones by decreasing iodide uptake [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"3rPSIFZZ","properties":{"formattedCitation":"(Agency for Toxic Substances and Disease Registry (ATSDR), 2008; Blount et al., 2006; NRC, 2005; Steinmaus et al., 2013; 2016)","plainCitation":"(Agency for Toxic Substances and Disease Registry (ATSDR), 2008; Blount et al., 2006; NRC, 2005; Steinmaus et al., 2013; 2016)","noteIndex":0},"citationItems":[{"id":428,"uris":["http://zotero.org/groups/945096/items/UIANA947"],"uri":["http://zotero.org/groups/945096/items/UIANA947"],"itemData":{"id":428,"type":"bill","title":"Toxicological Profile for Perchlorates","author":[{"literal":"Agency for Toxic Substances and Disease Registry (ATSDR)"}],"issued":{"date-parts":[["2008"]]}},"suppress-author":true,"prefix":"Agency for Toxic Substances and Disease Registry (ATSDR),"},{"id":203,"uris":["http://zotero.org/groups/945096/items/UW4TFPNI"],"uri":["http://zotero.org/groups/945096/items/UW4TFPNI"],"itemData":{"id":203,"type":"article-journal","title":"Urinary perchlorate and thyroid hormone levels in adolescent and adult men and

[4] For the purposes of this report, the term "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

women living in the United States","container-title":"Environmental Health Perspectives","page":"1865-1871","volume":"114","issue":"12","source":"CrossRef","DOI":"10.1289/ehp.9466","ISSN":"0091-6765","language":"en","author":[{"family":"Blount","given":"Benjamin C."},{"family":"Pirkle","given":"James L."},{"family":"Osterloh","given":"John D."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"Caldwell","given":"Kathleen L."}],"issued":{"date-parts":[["2006"]]}}},{"id":349,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":349,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"NRC"}],"issued":{"date-parts":[["2005"]]}}},{"id":39,"uris":["http://zotero.org/groups/945096/items/35VPNIKR"],"uri":["http://zotero.org/groups/945096/items/35VPNIKR"],"itemData":{"id":39,"type":"article-journal","title":"Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the national health and nutrition examination survey 2007-8","container-title":"Environmental research","volume":"123","source":"www.ncbi.nlm.nih.gov","abstract":"Perchlorate, thiocyanate, and low iodine intake can all decrease iodide intake into the thyroid gland. This can reduce thyroid hormone production since iodide is a key component of thyroid hormone. Previous research has suggested that each of these factors ...","URL":"https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857960/","DOI":"10.1016/j.envres.2013.01.005","note":"PMID: 23473920","language":"en","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Miller","given":"Mark D."},{"family":"Cushing","given":"Lara"},{"family":"Blount","given":"Benjamin C."},{"family":"Smith","given":"Allan H."}],"issued":{"date-parts":[["2013",5]]},"accessed":{"date-parts":[["2017",5,5]]}}},{"id":211,"uris":["http://zotero.org/groups/945096/items/H4FH49VS"],"uri":["http://zotero.org/groups/945096/items/H4FH49VS"],"itemData":{"id":211,"type":"article-journal","title":"Thyroid hormones and moderate exposure toperchlorate during pregnancy in women in southern California","container-title":"Environmental Health Perspectives","page":"861-867","volume":"124","issue":"6","source":"PubMed","abstract":"BACKGROUND: Findings from national surveys suggest that everyone in the United States is exposed to perchlorate. At high doses, perchlorate, thiocyanate, and nitrate inhibit iodide uptake into the thyroid and decrease thyroid hormone production. Small changes in thyroid hormones during pregnancy, including changes within normal reference ranges, have been linked to cognitive function declines in the offspring.\nOBJECTIVES: We evaluated the potential effects of low environmental exposures to perchlorate on thyroid function.\nMETHODS: Serum thyroid hormones and anti-thyroid antibodies and urinary perchlorate, thiocyanate, nitrate, and iodide concentrations were measured in 1,880 pregnant women from San Diego County, California, during 2000-2003, a period when much of the area's water supply was contaminated from an industrial plant with perchlorate at levels near the 2007 California regulatory standard of 6 μg/L. Linear regression was used to evaluate associations between urinary perchlorate and serum thyroid hormone concentrations in models adjusted for urinary creatinine and thiocyanate, maternal age and education, ethnicity, and gestational age at serum collection.\nRESULTS: The

median urinary perchlorate concentration was 6.5 μg/L, about two times higher than in the general U.S.\nPOPULATION: Adjusted associations were identified between increasing log10 perchlorate and decreasing total thyroxine (T4) [regression coefficient (β) = -0.70; 95% CI: -1.06, -0.34], decreasing free thyroxine (fT4) (β = -0.053; 95% CI: -0.092, -0.013), and increasing log10 thyroid-stimulating hormone (β = 0.071; 95% CI: 0.008, 0.133).\nCONCLUSIONS: These results suggest that environmental perchlorate exposures may affect thyroid hormone production during pregnancy. This could have implications for public health given widespread perchlorate exposure and the importance of thyroid hormone in fetal neurodevelopment.\nCITATION: Steinmaus C, Pearl M, Kharrazi M, Blount BC, Miller MD, Pearce EN, Valentin-Blasini L, DeLorenze G, Hoofnagle AN, Liaw J. 2016. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environ Health Perspect 124:861-867; http://dx.doi.org/10.1289/ehp.1409614.","DOI":"10.1289/ehp.1409614","ISSN":"1552-9924","note":"PMID: 26485730\nPMCID: PMC4892913","journalAbbreviation":"Environ. Health Perspect.","language":"eng","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Pearl","given":"Michelle"},{"family":"Kharrazi","given":"Martin"},{"family":"Blount","given":"Benjamin C."},{"family":"Miller","given":"Mark D."},{"family":"Pearce","given":"Elizabeth N."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"DeLorenze","given":"Gerald"},{"family":"Hoofnagle","given":"Andrew N."},{"family":"Liaw","given":"Jane"}],"issued":{"date-parts":[["2016",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. A reduction in T3 and T4 may also result in an increase in the thyroid stimulating hormone (TSH) as this hormone acts on the thyroid to increase the uptake of iodine in an effort to create more T3 and T4 based on a regulatory feedback mechanism. This mode of action (MOA) is supported by several advisory committee reports on perchlorate [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"RePjCjFr","properties":{"formattedCitation":"(NRC, 2005; SAB and USEPA, 2013)","plainCitation":"(NRC, 2005; SAB and USEPA, 2013)","noteIndex":0},"citationItems":[{"id":349,"uris":["http://zotero.org/groups/945096/items/TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":349,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National Academies Press","publisher-place":"Washington, DC","event-place":"Washington, DC","author":[{"literal":"NRC"}],"issued":{"date-parts":[["2005"]]}},"suppress-author":true,"prefix":"NRC,"},{"id":1263,"uris":["http://zotero.org/groups/945096/items/3MNU7GPK"],"uri":["http://zotero.org/groups/945096/items/3MNU7GPK"],"itemData":{"id":1263,"type":"article","title":"SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate. EPA-SAB-13-004","author":[{"literal":"SAB"},{"family":"USEPA","given":""}],"issued":{"date-parts":[["2013"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In 2005, the NRC evaluated the health implications of perchlorate exposure at the request of several Federal agencies. In their assessment, the NRC proposed an MOA that followed perchlorate exposure to reduced iodine intake, reduced serum T3 and T4, increased TSH, and subsequently to the adverse effect of hypothyroidism. Hypothyroidism is defined as increased TSH and decreased T4 to concentrations outside of their reference ranges. In support of the EPA

Office of Water's analyses related to perchlorate, the EPA's SAB reviewed the current state of the science on perchlorate and thyroid physiology in 2013 and largely supported the NRC's MOA, but revised it to include hypothyroxinemia as an additional outcome to consider [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CdXI5Naz","properties":{"formattedCitation":"(SAB for the U.S. EPA & U. S. Environmental Protection Agency, 2013)","plainCitation":"(SAB for the U.S. EPA & U. S. Environmental Protection Agency, 2013)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":"5Cn20MPv/gQaELIao","uris":["http://zotero.org/groups/945096/items/RVTWTXQR"],"uri":["http://zotero.org/groups/945096/items/RVTWTXQR"],"itemData":{"id":336,"type":"article","title":"SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate. EPA-SAB-13-004","author":[{"literal":"SAB for the U.S. EPA"},{"family":"U. S. Environmental Protection Agency","given":""}],"issued":{"date-parts":[["2013"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}][ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"gRrbuWUo","properties":{"formattedCitation":"(SAB and USEPA, 2013)","plainCitation":"(SAB and USEPA, 2013)","noteIndex":0},"citationItems":[{"id":1263,"uris":["http://zotero.org/groups/945096/items/3MNU7GPK"],"uri":["http://zotero.org/groups/945096/items/3MNU7GPK"],"itemData":{"id":1263,"type":"article","title":"SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate. EPA-SAB-13-004","author":[{"literal":"SAB"},{"family":"USEPA","given":""}],"issued":{"date-parts":[["2013"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Hypothyroxinemia is a condition that is defined as free T4 (fT4; T4 that is not bound to a protein) levels in the lower end of the reference range and normal TSH concentrations; it is not currently a medically treated condition. Both maternal hypothyroxinemia and maternal hypothyroidism during pregnancy have been associated with adverse neurodevelopmental outcomes (i.e., abnormal fetal and child development). [REF _Ref522634718 \h] presents both the NRC original and SAB modified MOA of perchlorate's thyroid-related adverse health effects.

When the NRC conducted its review of the health effects of perchlorate exposure in 2005, it stated that although none of the steps that follow iodine uptake inhibition in the MOA have been clearly observed in humans, they are biologically plausible (these are demonstrated with the dotted arrows in [REF _Ref522634718 \h * MERGEFORMAT]). Since the 2005 NRC report was published, however, several epidemiological studies have demonstrated an association between perchlorate exposure and changes in serum thyroid hormone levels [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"qZgStztL","properties":{"formattedCitation":"(Blount et al., 2006; Steinmaus et al., 2013; 2016)","plainCitation":"(Blount et al., 2006; Steinmaus et al., 2013; 2016)","noteIndex":0},"citationItems":[{"id":203,"uris":["http://zotero.org/groups/945096/items/UW4TFPNI"],"uri":["http://zotero.org/groups/945096/items/UW4TFPNI"],"itemData":{"id":203,"type":"article-journal","title":"Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States","container-title":"Environmental Health Perspectives","page":"1865-

1871","volume":"114","issue":"12","source":"CrossRef","DOI":"10.1289/ehp.9466","ISSN":"00
91-6765","language":"en","author":[{"family":"Blount","given":"Benjamin
C."},{"family":"Pirkle","given":"James L."},{"family":"Osterloh","given":"John
D."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"Caldwell","given":"Kathleen
L."}],"issued":{"date-
parts":[["2006"]]}}},{"id":39,"uris":["http://zotero.org/groups/945096/items/35VPNIKR"],"uri":
["http://zotero.org/groups/945096/items/35VPNIKR"],"itemData":{"id":39,"type":"article-
journal","title":"Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in
the national health and nutrition examination survey 2007-8","container-title":"Environmental
research","volume":"123","source":"www.ncbi.nlm.nih.gov","abstract":"Perchlorate,
thiocyanate, and low iodine intake can all decrease iodide intake into the thyroid gland. This can
reduce thyroid hormone production since iodide is a key component of thyroid hormone.
Previous research has suggested that each of these factors
...","URL":"https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857960/","DOI":"10.1016/j.envres
.2013.01.005","note":"PMID:
23473920","language":"en","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Miller
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D."},{"family":"Cushing","given":"Lara"},{"family":"Blount","given":"Benjamin
C."},{"family":"Smith","given":"Allan H."}],"issued":{"date-
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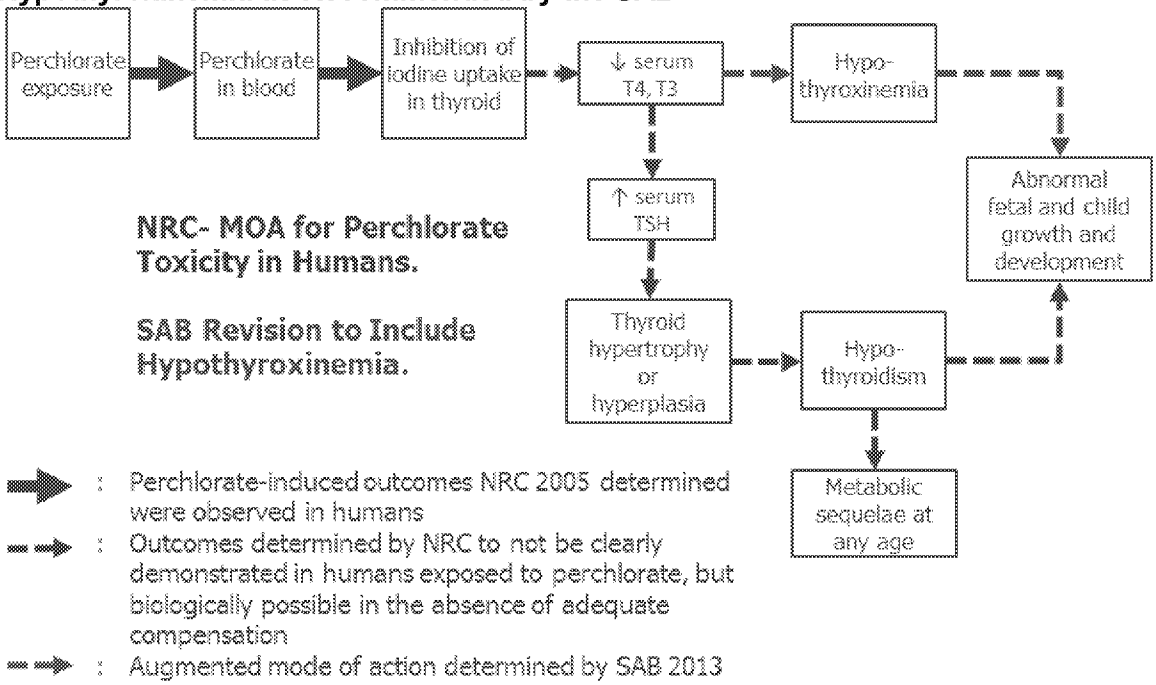
"uri":["http://zotero.org/groups/945096/items/H4FH49VS"],"itemData":{"id":211,"type":"article
-journal","title":"Thyroid hormones and moderate exposure toperchlorate during pregnancy in
women in southern California","container-title":"Environmental Health
Perspectives","page":"861-
867","volume":"124","issue":"6","source":"PubMed","abstract":"BACKGROUND: Findings
from national surveys suggest that everyone in the United States is exposed to perchlorate. At
high doses, perchlorate, thiocyanate, and nitrate inhibit iodide uptake into the thyroid and
decrease thyroid hormone production. Small changes in thyroid hormones during pregnancy,
including changes within normal reference ranges, have been linked to cognitive function
declines in the offspring.\nOBJECTIVES: We evaluated the potential effects of low
environmental exposures to perchlorate on thyroid function.\nMETHODS: Serum thyroid
hormones and anti-thyroid antibodies and urinary perchlorate, thiocyanate, nitrate, and iodide
concentrations were measured in 1,880 pregnant women from San Diego County, California,
during 2000-2003, a period when much of the area's water supply was contaminated from an
industrial plant with perchlorate at levels near the 2007 California regulatory standard of 6 μg/L.
Linear regression was used to evaluate associations between urinary perchlorate and serum
thyroid hormone concentrations in models adjusted for urinary creatinine and thiocyanate,
maternal age and education, ethnicity, and gestational age at serum collection.\nRESULTS: The
median urinary perchlorate concentration was 6.5 μg/L, about two times higher than in the
general U.S.\nPOPULATION: Adjusted associations were identified between increasing log10
perchlorate and decreasing total thyroxine (T4) [regression coefficient (β) = -0.70; 95% CI: -
1.06, -0.34], decreasing free thyroxine (fT4) (β = -0.053; 95% CI: -0.092, -0.013), and increasing
log10 thyroid-stimulating hormone (β = 0.071; 95% CI: 0.008, 0.133).\nCONCLUSIONS: These
results suggest that environmental perchlorate exposures may affect thyroid hormone production
during pregnancy. This could have implications for public health given widespread perchlorate

exposure and the importance of thyroid hormone in fetal neurodevelopment.\nCITATION: Steinmaus C, Pearl M, Kharrazi M, Blount BC, Miller MD, Pearce EN, Valentin-Blasini L, DeLorenze G, Hoofnagle AN, Liaw J. 2016. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environ Health Perspect 124:861-867; http://dx.doi.org/10.1289/ehp.1409614.","DOI":"10.1289/ehp.1409614","ISSN":"1552-9924","note":"PMID: 26485730\nPMCID: PMC4892913","journalAbbreviation":"Environ. Health Perspect.","language":"eng","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Pearl","given":"Michelle"},{"family":"Kharrazi","given":"Martin"},{"family":"Blount","given":"Benjamin C."},{"family":"Miller","given":"Mark D."},{"family":"Pearce","given":"Elizabeth N."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"DeLorenze","given":"Gerald"},{"family":"Hoofnagle","given":"Andrew N."},{"family":"Liaw","given":"Jane"}],"issued":{"date-parts":[["2016",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, Taylor et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"WG3FLDuE","properties":{"formattedCitation":"(2014)","plainCitation":"(2014)","noteIndex":0},"citationItems":[{"id":80,"uris":["http://zotero.org/groups/945096/items/F5PDEYCL"],"uri":["http://zotero.org/groups/945096/items/F5PDEYCL"],"itemData":{"id":80,"type":"article-journal","title":"Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring: data from the controlled antenatal thyroid study","container-title":"The Journal of Clinical Endocrinology & Metabolism","page":"4291-4298","volume":"99","issue":"11","ISSN":"0021-972X","author":[{"family":"Taylor","given":"P."},{"family":"Okosieme","given":"Onyebuchi E."},{"family":"Murphy","given":"Rhian"},{"family":"Hales","given":"C."},{"family":"Chiusano","given":"Elisabetta"},{"family":"Maina","given":"Aldo"},{"family":"Joomun","given":"Mohamed"},{"family":"Bestwick","given":"Jonathan P."},{"family":"Smyth","given":"Peter"},{"family":"Paradice","given":"Ruth"}],"issued":{"date-parts":[["2014"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] demonstrated the association between high maternal perchlorate exposure and risk of low IQ in offspring.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Modified Representation of NRC's Suggested MOA for Perchlorate Toxicity in Humans Indicating First Adverse Effect in the Continuum of Perchlorate Exposure to Effect, Revised to Include Hypothyroxinemia as Recommended by the SAB



As such, the EPA drew on the MOA proposed by the SAB to estimate benefits from reduced perchlorate exposure as a result of an NPDWR, which is now supported by several epidemiological studies [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"tvXUnpqQ","properties":{"formattedCitation":"(e.g., Blount et al., 2007; Steinmaus et al., 2016)","plainCitation":"(e.g., Blount et al., 2007; Steinmaus et al., 2016)","noteIndex":0},"citationItems":[{"id":264,"uris":["http://zotero.org/groups/945096/items/R9T25QKS"],"uri":["http://zotero.org/groups/945096/items/R9T25QKS"],"itemData":{"id":264,"type":"article-journal","title":"Perchlorate exposure of the US population, 2001–2002","container-title":"Journal of Exposure Science and Environmental Epidemiology","page":"400–407","volume":"17","issue":"4","source":"Google Scholar","author":[{"family":"Blount","given":"Benjamin C."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"Osterloh","given":"John D."},{"family":"Mauldin","given":"Joshua P."},{"family":"Pirkle","given":"James L."}],"issued":{"date-parts":[["2007"]]}},"prefix":"e.g., "},{"id":211,"uris":["http://zotero.org/groups/945096/items/H4FH49VS"],"uri":["http://zotero.org/groups/945096/items/H4FH49VS"],"itemData":{"id":211,"type":"article-journal","title":"Thyroid hormones and moderate exposure toperchlorate during pregnancy in women in southern California","container-title":"Environmental Health Perspectives","page":"861-867","volume":"124","issue":"6","source":"PubMed","abstract":"BACKGROUND: Findings from national surveys suggest that everyone in the United States is exposed to perchlorate. At high doses, perchlorate, thiocyanate, and nitrate inhibit iodide uptake into the thyroid and decrease thyroid hormone production. Small changes in thyroid hormones during pregnancy,

including changes within normal reference ranges, have been linked to cognitive function declines in the offspring.\nOBJECTIVES: We evaluated the potential effects of low environmental exposures to perchlorate on thyroid function.\nMETHODS: Serum thyroid hormones and anti-thyroid antibodies and urinary perchlorate, thiocyanate, nitrate, and iodide concentrations were measured in 1,880 pregnant women from San Diego County, California, during 2000-2003, a period when much of the area's water supply was contaminated from an industrial plant with perchlorate at levels near the 2007 California regulatory standard of 6 μg/L. Linear regression was used to evaluate associations between urinary perchlorate and serum thyroid hormone concentrations in models adjusted for urinary creatinine and thiocyanate, maternal age and education, ethnicity, and gestational age at serum collection.\nRESULTS: The median urinary perchlorate concentration was 6.5 μg/L, about two times higher than in the general U.S.\nPOPULATION: Adjusted associations were identified between increasing log10 perchlorate and decreasing total thyroxine (T4) [regression coefficient (β) = -0.70; 95% CI: -1.06, -0.34], decreasing free thyroxine (fT4) (β = -0.053; 95% CI: -0.092, -0.013), and increasing log10 thyroid-stimulating hormone (β = 0.071; 95% CI: 0.008, 0.133).\nCONCLUSIONS: These results suggest that environmental perchlorate exposures may affect thyroid hormone production during pregnancy. This could have implications for public health given widespread perchlorate exposure and the importance of thyroid hormone in fetal neurodevelopment.\nCITATION: Steinmaus C, Pearl M, Kharrazi M, Blount BC, Miller MD, Pearce EN, Valentin-Blasini L, DeLorenze G, Hoofnagle AN, Liaw J. 2016. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environ Health Perspect 124:861-867; http://dx.doi.org/10.1289/ehp.1409614.","DOI":"10.1289/ehp.1409614","ISSN":"1552-9924","note":"PMID: 26485730\nPMCID: PMC4892913","journalAbbreviation":"Environ. Health Perspect.","language":"eng","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Pearl","given":"Michelle"},{"family":"Kharrazi","given":"Martin"},{"family":"Blount","given":"Benjamin C."},{"family":"Miller","given":"Mark D."},{"family":"Pearce","given":"Elizabeth N."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"DeLorenze","given":"Gerald"},{"family":"Hoofnagle","given":"Andrew N."},{"family":"Liaw","given":"Jane"}],"issued":{"date-parts":[["2016",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The EPA took a two-step approach to relate perchlorate exposure to changes in a quantifiable health endpoint. Specifically, the EPA related changes in perchlorate to changes in thyroid hormones in a mother using a BBDR model, and applied the resulting changes in thyroid hormones to changes in IQ in her offspring using dose-response functions derived from the peer-reviewed literature [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"9vxa6n5e","properties":{"formattedCitation":"(USEPA, 2018e)","plainCitation":"(USEPA, 2018e)","noteIndex":0},"citationItems":[{"id":926,"uris":["http://zotero.org/groups/945096/items/ANBBTDKU"],"uri":["http://zotero.org/groups/945096/items/ANBBTDKU"],"itemData":{"id":926,"type":"report","title":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","shortTitle":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}]. This analysis is underpinned by the appreciable evidence that maternal hypothyroxinemia during pregnancy is related to adverse neurodevelopmental outcomes in offspring [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"zPUvJteB","properties":{"formattedCitation":"(Alexander et al., 2017; Ghassabian et al., 2011; Gyllenberg et al., 2016; Henrichs et al., 2010; Noten et al., 2015; Pop et al., 2003; 1999; Rom\\uc0\\u225{}n et al., 2013; SAB and USEPA, 2013; van Mil et al., 2012)","plainCitation":"(Alexander et al., 2017; Ghassabian et al., 2011; Gyllenberg et al., 2016; Henrichs et al., 2010; Noten et al., 2015; Pop et al., 2003; 1999; Román et al., 2013; SAB and USEPA, 2013; van Mil et al., 2012)","noteIndex":0},"citationItems":[{"id":436,"uris":["http://zotero.org/groups/945096/items/PI246VF6"],"uri":["http://zotero.org/groups/945096/items/PI246VF6"],"itemData":{"id":436,"type":"article-journal","title":"2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum","container-title":"Thyroid","page":"315-389","volume":"27","issue":"3","author":[{"family":"Alexander","given":"E. K."},{"family":"Pearce","given":"E. N."},{"family":"Brent","given":"G. A."},{"family":"Brown","given":"R. S."},{"family":"Chen","given":"H."},{"family":"Dosiou","given":"C."},{"family":"Sullivan","given":"S."}],"issued":{"date-parts":[["2017"]]}}},{"id":394,"uris":["http://zotero.org/groups/945096/items/8H54TCGT"],"uri":["http://zotero.org/groups/945096/items/8H54TCGT"],"itemData":{"id":394,"type":"article-journal","title":"Maternal thyroid function during pregnancy and behavioral problems in the offspring: The Generation R Study","container-title":"Pediatric Research","volume":"69","issue":"5","author":[{"family":"Ghassabian","given":"A."},{"family":"Bongers-Schokking JJ","given":""},{"family":"Henrichs","given":"J."},{"family":"Jaddoe","given":"V. W."},{"family":"Visser","given":"T. J."}],"issued":{"date-parts":[["2011"]]}}},{"id":24,"uris":["http://zotero.org/groups/945096/items/937P2NGT"],"uri":["http://zotero.org/groups/945096/items/937P2NGT"],"itemData":{"id":24,"type":"article-journal","title":"Hypothyroxinemia during gestation and offspring schizophrenia in a national birth cohort","container-title":"Biological Psychiatry","page":"962-970","volume":"79","issue":"12","source":"PubMed","abstract":"BACKGROUND: Evidence from animal and human studies indicates that thyroid hormone deficiency during early gestation alters brain development. As schizophrenia is associated with prenatal brain insults and premorbid cognitive deficits, we tested the a priori hypothesis that serologically defined maternal thyroid deficiency during early gestation to mid-gestation is associated with schizophrenia in offspring.\nMETHODS: The investigation is based on the Finnish Prenatal Study of Schizophrenia, a nested case-control study that included archived maternal sera from virtually all pregnancies since 1983 (N = >1 million). We identified all offspring in the cohort with a diagnosis of schizophrenia based on the national inpatient and outpatient register and matched them on sex, date of birth, and residence in Finland at time of onset of the case to comparison subjects (1:1) from the cohort. Maternal sera of 1010 case-control pairs were assessed for free thyroxine, and sera of 948 case-control pairs were assessed for thyroid-stimulating hormone.\nRESULTS: Maternal hypothyroxinemia (free thyroxine ≤10th percentile, normal thyroid-stimulating hormone) was associated with an increased odds of schizophrenia (odds ratio = 1.75, 95% confidence interval = 1.22-2.50, p = .002). When adjusted for maternal psychiatric

history, province of birth, and maternal smoking during pregnancy, the association remained significant (odds ratio = 1.70, 95% confidence interval = 1.13-2.55, p = .010).\nCONCLUSIONS: In a large, national birth cohort, prospectively documented hypothyroxinemia during early gestation to mid-gestation was associated with increased odds of schizophrenia in offspring. This information can inform translational studies of maternal hypothyroxinemia examining molecular and cellular deviations relevant to schizophrenia.","DOI":"10.1016/j.biopsych.2015.06.014","ISSN":"1873-2402","note":"PMID: 26194598\nPMCID: PMC4684794","journalAbbreviation":"Biol. Psychiatry","language":"eng","author":[{"family":"Gyllenberg","given":"David"},{"family":"Sourander","given":"Andre"},{"family":"Surcel","given":"Heljä-Marja"},{"family":"Hinkka-Yli-Salomäki","given":"Susanna"},{"family":"McKeague","given":"Ian W."},{"family":"Brown","given":"Alan S."}],"issued":{"date-parts":[["2016",6,15]]}}},{"id":383,"uris":["http://zotero.org/groups/945096/items/NZRKVAQJ"],"uri":["http://zotero.org/groups/945096/items/NZRKVAQJ"],"itemData":{"id":383,"type":"article-journal","title":"Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study","container-title":"Journal of Clinical Endocrinology and Metabolism","page":"4227-4234","volume":"95","issue":"9","DOI":"10.1210/jc.2010-0415","author":[{"family":"Henrichs","given":"J."},{"family":"Bongers-Schokking","given":"J. J."},{"family":"Schenk","given":"J. J."},{"family":"Ghassabian","given":"A."},{"family":"Schmidt","given":"H. G."},{"family":"Visser","given":"T. J."},{"family":"Hooijkaas","given":"H."},{"family":"Muinck Keizer-Schrama","given":"S. M. P. F.","non-dropping-particle":"de"},{"family":"Hofman","given":"A."},{"family":"Jaddo","given":"V. V. W."},{"family":"Visser","given":"W."},{"family":"Steegers","given":"E. A. P."},{"family":"Verhulst","given":"F. C."},{"family":"Rijke","given":"Y. B.","non-dropping-particle":"de"},{"family":"Tiemeier","given":"H."}],"issued":{"date-parts":[["2010"]]}}},{"id":10,"uris":["http://zotero.org/groups/945096/items/I9KUUQIF"],"uri":["http://zotero.org/groups/945096/items/I9KUUQIF"],"itemData":{"id":10,"type":"article-journal","title":"Maternal hypothyroxinaemia in early pregnancy and school performance in 5-year-old offspring","container-title":"European Journal of Endocrinology","page":"563-571","volume":"173","issue":"5","source":"PubMed","abstract":"OBJECTIVE: Overt hypothyroidism in pregnant women is associated with a lower intelligence quotient in their children. More recently, subtle decreases in maternal thyroid function have also been associated with neurodevelopmental impairment in offspring. We tested the effect of hypothyroxinaemia during early pregnancy on school performance.\nDESIGN: This was a longitudinal study that included the data of 1196 mother-child pairs from the Amsterdam Born Children and Their Development study.\nMETHODS: Maternal serum free thyroxine (T4) and TSH were obtained at a median gestational age of 12.9 (interquartile range: 11.9-14.3) weeks. School performance was assessed at age 5 years and based on scores obtained in arithmetic and language tests from the national monitoring and evaluation system. Poor school performance was defined as a test result <25th percentile and subnormal school performance as a result <50th percentile of the norm population. To estimate the impact of possible non-response bias, we conducted inverse-probability weighted analyses.\nRESULTS: Maternal hypothyroxinaemia (i.e., a maternal free T4 in the lowest 10% of distribution) was associated with a 1.61 (95% CI: 1.05-2.47) -fold increased odds of subnormal arithmetic performance after adjustment for confounders (P=0.03).

However, the odds ratio dropped to 1.48 (95% CI: 0.94-2.32) after inverse-probability weighting (P=0.09). No such relations were found with TSH.\nCONCLUSIONS: Maternal hypothyroxinaemia at the end of the first trimester was associated with reduced performance in an arithmetic test, but not in a language test, in 5-year-old offspring. However, our results should be interpreted carefully because of possible non-response bias.","DOI":"10.1530/EJE-15-0397","ISSN":"1479-683X","note":"PMID: 26306579","journalAbbreviation":"Eur. J. Endocrinol.","language":"eng","author":[{"family":"Noten","given":"Anna M. E."},{"family":"Loomans","given":"Eva M."},{"family":"Vrijkotte","given":"Tanja G. M."},{"family":"Ven","given":"Peter M.","non-dropping-particle":"van de"},{"family":"Trotsenburg","given":"A. S. Paul","non-dropping-particle":"van"},{"family":"Rotteveel","given":"Joost"},{"family":"Eijsden","given":"Manon","non-dropping-particle":"van"},{"family":"Finken","given":"Martijn J. J."}],"issued":{"date-parts":[["2015",11]]}}},{"id":198,"uris":["http://zotero.org/groups/945096/items/WKCD55DW"],"uri":["http://zotero.org/groups/945096/items/WKCD55DW"],"itemData":{"id":198,"type":"article-journal","title":"Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study","container-title":"Clinical Endocrinology","page":"282-288","volume":"59","issue":"3","source":"PubMed","abstract":"OBJECTIVE: To evaluate the impact of maternal hypothyroxinaemia during early gestation (fT4 below the lowest tenth percentile and TSH within the reference range: 0.15-2.0 mIU/l) on infant development, together with any subsequent changes in fT4 during gestation.\nDESIGN: A prospective 3-year follow-up study of pregnant women and their children up to the age of 2 years.\nMEASUREMENTS: Child development was assessed by means of the Bayley Scales of Infant Development in children of women with hypothyroxinaemia (fT4 below the tenth percentile at 12 weeks' gestation) at 12 weeks' gestation (cases), and in children of women with fT4 between the 50th and 90th percentiles at 12 weeks' gestation, matched for parity and gravidity (controls). Maternal thyroid function (fT4 and TSH) was assessed at 12, 24 and 32 weeks' gestation. The mental and motor function of 63 cases and 62 controls was compared at the age of 1 year, and of 57 cases and 58 controls at the age of 2 years.\nRESULTS: Children of women with hypothyroxinaemia at 12 weeks' gestation had delayed mental and motor function compared to controls: 10 index points on the mental scale (95% CI: 4.5-15 points, P = 0.003) and eight on the motor scale at the age of 1 year (95% CI: 2.3-12.8 points, P = 0.02), as well as eight index points on the mental (95% CI: 4-12 points, P = 0.02), and 10 on the motor scale (95%CI: 6-16 points, P = 0.005) at the age of 2 years. Children of hypothyroxinaemic women in whom the fT4 concentration was increased at 24 and 32 weeks' gestation had similar scores to controls, while in the controls, the developmental scores were not influenced by further declines in maternal fT4 at 24 and 32 weeks' gestation.\nCONCLUSIONS: Maternal hypothyroxinaemia during early gestation is an independent determinant of a delay in infant neurodevelopment. However, when fT4 concentrations increase during pregnancy in women who are hypothyroxinaemic during early gestation, infant development appears not to be adversely affected.","ISSN":"0300-0664","note":"PMID: 12919150","shortTitle":"Maternal hypothyroxinaemia during early pregnancy and subsequent child development","journalAbbreviation":"Clin. Endocrinol. (Oxf)","language":"eng","author":[{"family":"Pop","given":"Victor J."},{"family":"Brouwers","given":"Evelien P."},{"family":"Vader","given":"Huib L."},{"family":"Vulsma","given":"Thomas"},{"family":"Baar","given":"Anneloes L.","non-dropping-particle":"van"},{"family":"Vijlder","given":"Jan J.","non-dropping-particle":"de"}],"issued":{"date-

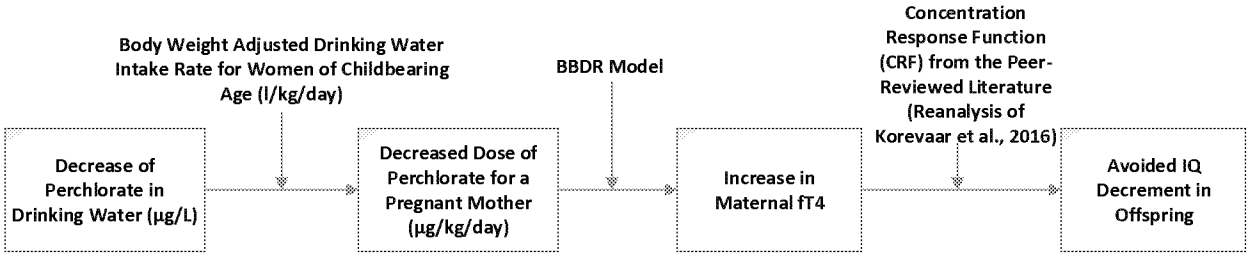
parts":[["2003",9]]}}},{"id":13,"uris":["http://zotero.org/groups/945096/items/VERVX5Q7"],"uri":["http://zotero.org/groups/945096/items/VERVX5Q7"],"itemData":{"id":13,"type":"article-journal","title":"Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy","container-title":"Clinical Endocrinology","page":"149-155","volume":"50","issue":"2","source":"PubMed","abstract":"BACKGROUND: Maternal thyroid function during early pregnancy is an important determinant of early fetal brain development because the fetal thyroid is unable to produce any T4 before 12-14 weeks' gestation. Overt maternal hypothyroidism as seen in severe iodine-deficient areas is associated with severely impaired neurological development of the offspring. At present, it is not known whether low free T4 (fT4) levels during pregnancy in healthy women from iodine sufficient areas may affect fetal neurodevelopment.\nMETHODS: Neurodevelopment was assessed at 10 months of age in a cohort of 220 healthy children, born after uncomplicated pregnancies and deliveries, using the Bayley Scales of Infant Development. Maternal TSH, fT4 and TPO antibody status were assessed at 12 and 32 weeks' gestation. Maternal gestational fT4 concentration was defined as an independent parameter for child development.\nRESULTS: Children of women with fT4 levels below the 5th (< 9.8 pmol/l, n = 11) and 10th (< 10.4 pmol/l, n = 22) percentiles at 12 weeks' gestation had significantly lower scores on the Bayley Psychomotor Developmental Index (PDI) scale at 10 months of age, compared to children of mothers with higher fT4 values (t test, mean difference: 14.1, 95% confidence interval (CI): 5.9-22 and 7.4, 95% CI: 1.1-13.9, respectively). At 32 weeks' gestation, no significant differences were found. In the group of women with the lowest 10th percentile fT4 concentrations at 12 weeks' gestation, a positive correlation was found between the mothers' fT4 concentration and children's PDI scores (linear regression, R: 0.46, P = 0.03). After correction for confounding variables, a fT4 concentration below the 10th percentile at 12 weeks' gestation was a significant risk factor for impaired psychomotor development (RR): 5.8, 95% CI: 1.3-12.6).\nCONCLUSIONS: Low maternal plasma fT4 concentrations during early pregnancy may be an important risk factor for impaired infant development.","ISSN":"0300-0664","note":"PMID: 10396355","journalAbbreviation":"Clin. Endocrinol. (Oxf)","language":"eng","author":[{"family":"Pop","given":"Victor J."},{"family":"Kuijpens","given":"J. L."},{"family":"Baar","given":"A. L.","non-dropping-particle":"van"},{"family":"Verkerk","given":"G."},{"family":"Son","given":"M. M.","non-dropping-particle":"van"},{"family":"Vijlder","given":"J. J.","non-dropping-particle":"de"},{"family":"Vulsma","given":"T."},{"family":"Wiersinga","given":"W. M."},{"family":"Drexhage","given":"H. A."},{"family":"Vader","given":"H. L."}],"issued":{"date-parts":[["1999",2]]}}},{"id":94,"uris":["http://zotero.org/groups/945096/items/3W4UTVXX"],"uri":["http://zotero.org/groups/945096/items/3W4UTVXX"],"itemData":{"id":94,"type":"article-journal","title":"Association of gestational maternal hypothyroxinemia and increased autism risk","container-title":"Annals of Neurology","page":"733-742","volume":"74","issue":"5","DOI":"10.1002/ana.23976","author":[{"family":"Román","given":"G. C."},{"family":"Ghassabian","given":"A."},{"family":"Bongers-Schokking","given":"J."},{"family":"Jaddoe","given":"V. W. V."},{"family":"Hofman","given":"A."},{"family":"Rijke","given":"Y. B.","non-dropping-particle":"de"},{"family":"Verhulst","given":"F. C."},{"family":"Tiemeier","given":"H."}],"issued":{"date-

parts":[["2013"]]}},{"id":1263,"uris":["http://zotero.org/groups/945096/items/3MNU7GPK"],"uri":["http://zotero.org/groups/945096/items/3MNU7GPK"],"itemData":{"id":1263,"type":"article","title":"SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate. EPA-SAB-13-004","author":[{"literal":"SAB"},{"family":"USEPA","given":""}],"issued":{"date-parts":[["2013"]]}},{"id":68,"uris":["http://zotero.org/groups/945096/items/ICMQPI5W"],"uri":["http://zotero.org/groups/945096/items/ICMQPI5W"],"itemData":{"id":68,"type":"article-journal","title":"Maternal hypothryoxinemia during pregnancy and growth of the fetal and infant head","container-title":"Reproductive Sciences","page":"1315-1322","volume":"19","issue":"12","DOI":"10.1177/1933719112450338","author":[{"family":"Mil","given":"N. H.","non-dropping-particle":"van"},{"family":"Steegers-Theunissen","given":"Regine P. M."},{"family":"Bongers-Schokking","given":"Jacoba J."},{"family":"El Marroun","given":"Hanan"},{"family":"Ghassabian","given":"Akhgar"},{"family":"Hofman","given":"Albert"},{"family":"Jaddoe","given":"Vincent W. V."},{"family":"Verhulst","given":"Frank C."},{"family":"Rijke","given":"Yolanda B.","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A. P."},{"family":"Tiemeier","given":"Henning"}],"issued":{"date-parts":[["2012"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This evidence demonstrates that minor perturbations in maternal thyroid hormones, in what would be considered a "normal range," can result in altered neurodevelopmental outcomes in offspring, including decreased IQ. This multi-step approach was evaluated by a peer-review panel in the context of setting an MCLG in January 2018 and was well-received [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"QVYgJ2s6","properties":{"formattedCitation":"(External Peer Reviewers for USEPA, 2018)","plainCitation":"(External Peer Reviewers for USEPA, 2018)","noteIndex":0},"citationItems":[{"id":184,"uris":["http://zotero.org/groups/945096/items/EZ4C5CRT"],"uri":["http://zotero.org/groups/945096/items/EZ4C5CRT"],"itemData":{"id":184,"type":"article","title":"External peer review for U.S. EPA's proposed approaches to inform the derivation of a maximum contaminant level goal for perchlorate in drinking water","author":[{"literal":"External Peer Reviewers for USEPA"}],"issued":{"date-parts":[["2018"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

[REF _Ref522614073 \h] summarizes the approach taken to evaluate the benefits of changes in IQ as a result of a reduction in perchlorate exposure due to the proposed MCLs. IQ is the only endpoint currently being monetized in this economic analysis. The EPA has deemed perchlorate not likely to be carcinogenic to humans [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UtjLzmMG","properties":{"formattedCitation":"(2005b)","plainCitation":"(2005b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1007,"uris":["http://zotero.org/groups/945096/items/LHANJBR6"],"uri":["http://zotero.org/groups/945096/items/LHANJBR6"],"itemData":{"id":1007,"type":"article","title":"Integrated Risk Information System (IRIS) Chemical Assessment Summary: Perchlorate (ClO4-) and Perchlorate Salts","publisher":"USEPA National Center for Environmental Assessment","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and subsequently no cancer endpoints have

been assessed. Additional benefits that may arise from reducing perchlorate exposure but could not be monetized are discussed in Section [REF _Ref523397403 \n \h].

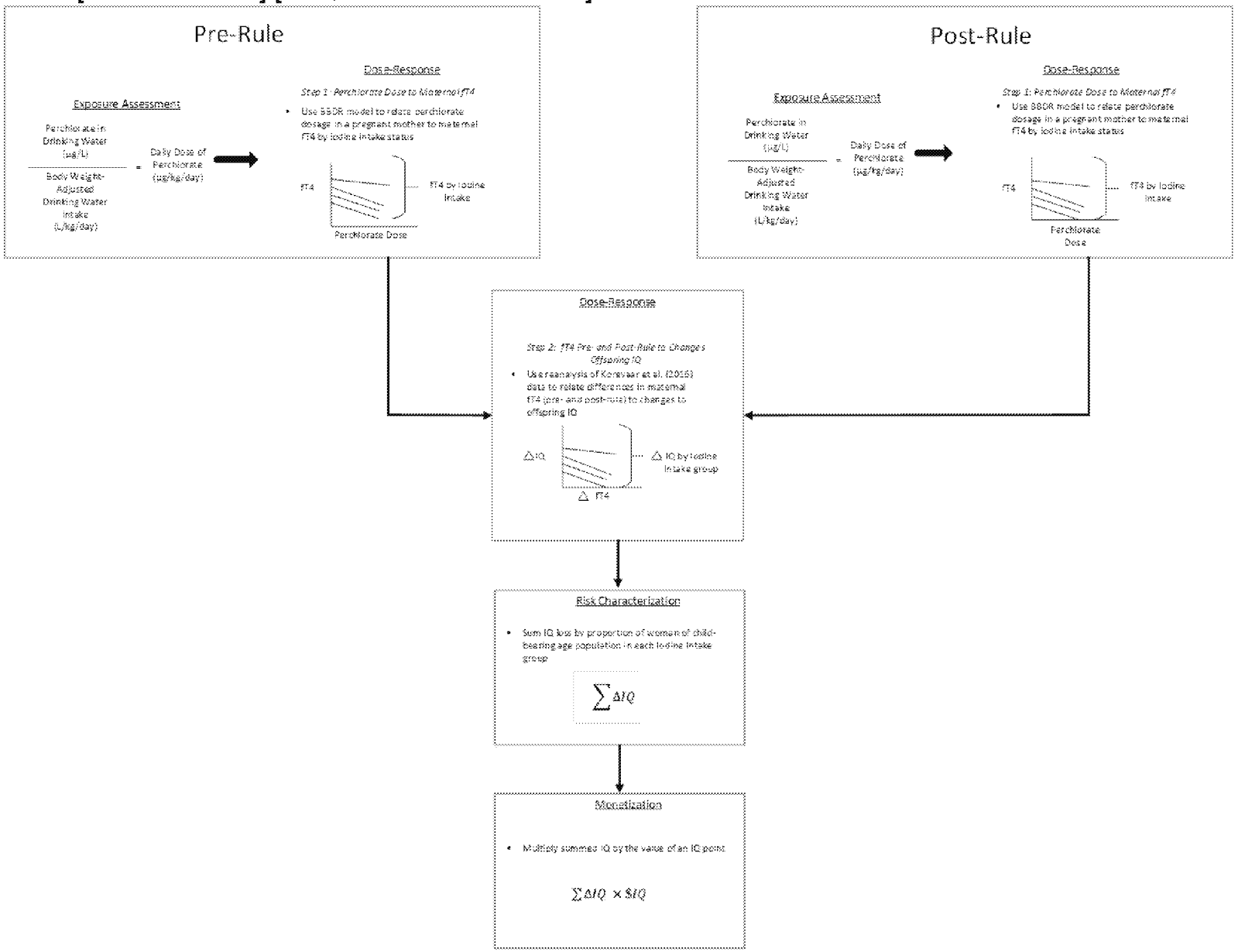
Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Overview of the Approach for Estimating Changes in IQ in Offspring from Reduced Perchlorate Exposure in a Pregnant Mother



4.2 Quantitative Benefits Assessment

As outlined in [REF _Ref522614073 \h], the EPA is utilizing a multi-step process to evaluate the human health-related impacts of perchlorate. [REF _Ref522697939 \h][REF _Ref523393377 \h] elaborates more on this process. The figure demonstrates that an analysis to determine pre- and post-rule exposures to perchlorate is conducted first, followed by a two-step dose-response analysis that relates pre- and post-rule perchlorate exposure to pre- and post-rule maternal fT4 levels, which is then translated to a change in offspring IQ and monetized. The dose-response relationship between perchlorate exposure and maternal fT4 is dependent on maternal iodine intake status, and as such this analysis is repeated for several categories of iodine intake. Ultimately, the change in IQ for all iodine intake groups is averaged based on the proportion of individuals in each iodine intake category. The total avoided IQ decrements on an annual basis is estimated over a 35-year timeframe used for the cost analysis described in Section 5. Additional details on each step of the benefits analysis are in subsequent sections.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Overview of Process to Estimate Benefits from Perchlorate Exposure



4.2.1 Exposure Assessment

To assess the benefits of reduced exposure to perchlorate in drinking water, the EPA must first define who is exposed and at what levels. Additionally, the EPA must also define and enumerate the population experiencing quantitative benefits due to the reduction in exposure. Therefore in this section the key inputs to understand who will be exposed, who will experience quantitative benefits, and the amount of perchlorate exposure in both pre- and post-rule scenarios are outlined.

4.2.1.1 Perchlorate Occurrence in U.S. Drinking Water

Section [REF _Ref523404705 \n \h] reports the current occurrence of perchlorate. As a reminder, [REF _Ref523449433 \h] and [REF _Ref523448716 \h] are repeated as [REF _Ref523404751 \h] and [REF _Ref523404750 \h]. These tables summarize the systems impacted when considering maximum perchlorate concentrations at 56 µg/L or 18 µg/L. The concentrations of perchlorate in these systems are the pre-rule exposure concentrations.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Expected Stage 1 Perchlorate Occurrence Greater than 56 µg/L

Affected Entity	Small Systems	Large Systems	Total Systems
Entry points	0	2	2
Population served	0	32,432	32,432
Water systems	0	2	2
Population served	0	64,733	64,733

Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"6Y8QVLMA","properties":{"formattedCitation":"(2018d)","plainCitation":"(2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Expected Stage 1 Perchlorate Occurrence Greater than 18 µg/L

Affected Entity	Small Systems	Large Systems	Total Systems
Entry points	1	16	17
Population served	2,155	618,406	620,560
Water systems	1	14	15
Population served	4,309	696,871	701,180

Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"sYgCheHc","properties":{"formattedCitation":"(2018d)","plainCitation":"(2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

For post-rule, the EPA assumed that any system exceeding an MCL will include a safety factor of 80 percent when implementing treatment (i.e., treat to 0.8 × MCL) to avoid future MCL exceedances.[5] Therefore, when considering systems that are at or above 18 µg/L, the system is assumed to design and implement treatment to achieve a target of 14.4 µg/L. If the MCL is 56 µg/L, the system is assumed to achieve a target of 44.8 µg/L.

4.2.1.2 Drinking Water Consumption Rates

The EPA Exposure Factors Handbook (EFH) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"EmVsXCy9","properties":{"formattedCitation":"(EPA, 2011b)","plainCitation":"(EPA, 2011b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":162,"uris":["http://zotero.org/groups/945096/items/8AZKGTHH"],"uri":["http://zotero.org/groups/945096/items/8AZKGTHH"],"itemData":{"id":162,"type":"report","title":"Exposure Factors Handbook 2011 Edition (Final Report)","page":"Chapter 8","abstract":"EPA announced the release of the final report, <i>Exposure Factors Handbook: 2011 Edition (EPA/600/R","URL":"https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252","language":"en","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2011"]]},"accessed":{"date-parts":[["2017",5,3]]}},"suppress-author":true,"prefix":"EPA,"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] reports mean, 90th, and 95th percentile bodyweight-adjusted drinking water intakes for pregnant, lactating, and non-pregnant non-lactating women of childbearing age. These figures are reported from the Kahn and Stralka [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rE57YWmU","properties":{"formattedCitation":"(2008)","plainCitation":"(2008)","noteIndex":0},"citationItems":[{"id":188,"uris":["http://zotero.org/groups/945096/items/JZJAVK6M"],"uri":["http://zotero.org/groups/945096/items/JZJAVK6M"],"itemData":{"id":188,"type":"article-journal","title":"Estimates of water ingestion for women in pregnant, lactating, and non-pregnant and non-lactating child-bearing age groups based on USDA's 1994–96, 1998 continuing survey of food intake by individuals","container-title":"Human and Ecological Risk Assessment: An International Journal","page":"1273-1290","volume":"14","issue":"6","DOI":"10.1080/10807030802494618","ISSN":"1080-7039","shortTitle":"Estimates of water ingestion for women in pregnant, lactating, and non-pregnant and non-lactating child-bearing age groups based on USDA's 1994–96, 1998 continuing survey of food intake by individuals","author":[{"family":"Kahn","given":"Henry

[5] Safety factors are commonly used, but the values can vary. For example, the 10 States Standards [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"zykqAnZL","properties":{"formattedCitation":"(Great Lakes - Upper Mississippi River Board of State and Provincial and Public Health and Environmental Managers, 2012)","plainCitation":"(Great Lakes - Upper Mississippi River Board of State and Provincial and Public Health and Environmental Managers, 2012)","noteIndex":5},"citationItems":[{"id":1262,"uris":["http://zotero.org/groups/945096/items/GNKJ3I8R"],"uri":["http://zotero.org/groups/945096/items/GNKJ3I8R"],"itemData":{"id":1262,"type":"article","title":"Recommended Standards for Water Works, 2012 ed.","author":[{"literal":"Great Lakes - Upper Mississippi River Board of State and Provincial"},{"literal":"Public Health and Environmental Managers"}],"issued":{"date-parts":[["2012"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] recommends design targets below MCLs, as low as 50 percent for arsenic treatment. The EPA selected 80 percent, which allows a 25 percent excursion from design performance while still achieving compliance.

D."},{"family":"Stralka","given":"Kathleen"}],"issued":{"date-parts":[["2008",11,21]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] study, which is based on the Continuing Survey of Food Intakes by Individuals (CSFII) data collected from 1994 to 1996 and 1998. This study estimated bodyweight-adjusted drinking water intake rates for direct and indirect community water ingestion, as well as for direct and indirect water intake from all sources, on both a per-capita and consumers-only basis. As the potential MCLs are specific for the offspring of pregnant women consuming community drinking water, the EPA chose to focus on community drinking water intake estimates on a consumers-only basis as potential inputs. These estimates are reported in Table 3-81 in the EFH [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"43y7oVIa","properties":{"formattedCitation":"(USEPA, 2011b)","plainCitation":"(USEPA, 2011b)","noteIndex":0},"citationItems":[{"id":162,"uris":["http://zotero.org/groups/945096/items/8AZKGTHH"],"uri":["http://zotero.org/groups/945096/items/8AZKGTHH"],"itemData":{"id":162,"type":"report","title":"Exposure Factors Handbook 2011 Edition (Final Report)","page":"Chapter 8","abstract":"EPA announced the release of the final report, <i>Exposure Factors Handbook: 2011 Edition (EPA/600/R","URL":"https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252","language":"en","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2011"]]},"accessed":{"date-parts":[["2017",5,3]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and are reproduced in [REF _Ref522614193 \h].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Consumers-Only Estimated Direct and Indirect Community Water Ingestion Rates from Kahn and Stralka (2008) (L/kg/day)

Women Categories	Sample Size	Mean	90th Percentile	95th Percentile
Pregnant[a]	65	0.014	0.033	0.043
Lactating[a]	33	0.026	0.054	0.055
Non-pregnant, non-lactating, 15 to 44 years of age	2,028	0.015	0.032	0.038

a. The sample size does not meet minimum reporting requirements to make statistically reliable estimates as described in the *Third Report on Nutrition Monitoring in the United States*, which covers 1994–1996 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"l59hN8ZE","properties":{"formattedCitation":"(FASEB/LSRO, 1995)","plainCitation":"(FASEB/LSRO, 1995)","noteIndex":0},"citationItems":[{"id":1040,"uris":["http://zotero.org/groups/945096/items/MN5AETQ4"],"uri":["http://zotero.org/groups/945096/items/MN5AETQ4"],"itemData":{"id":1040,"type":"report","title":"Third report on nutrition monitoring in the United States","publisher-place":"Washington, DC","event-place":"Washington, DC","URL":"https://www.cdc.gov/nchs/data/misc/nutri95_1acc.pdf","author":[{"literal":"FASEB/LSRO"}],"issued":{"date-parts":[["1995"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The EPA chose to use exposure factor estimates specific to women of childbearing age in conducting this benefits assessment for the proposed MCL (i.e., non-pregnant, non-lactating, 15–44 years of age). This determination was reached as the calibration of the BBDR model was performed using a population of women of childbearing age from the National Health and

Nutrition Examination Survey (NHANES). The EPA has chosen to apply the 90th percentile drinking water intake rate in order to remain consistent with the assumption made in supporting the derivation of the MCLG. Thus, according to Table 3-81 in the EFH [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"3qPpsryF","properties":{"formattedCitation":"(EPA, 2011b)","plainCitation":"(EPA, 2011b)","noteIndex":0},"citationItems":[{"id":162,"uris":["http://zotero.org/groups/945096/items/8AZKGTHH"],"uri":["http://zotero.org/groups/945096/items/8AZKGTHH"],"itemData":{"id":162,"type":"report","title":"Exposure Factors Handbook 2011 Edition (Final Report)","page":"Chapter 8","abstract":"EPA announced the release of the final report, <i>Exposure Factors Handbook: 2011 Edition (EPA/600/R","URL":"https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252","language":"en","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2011"]]},"accessed":{"date-parts":[["2017",5,3]]}},"suppress-author":true,"prefix":"EPA,"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the bodyweight-adjusted drinking water intake rate for women of childbearing age is 0.032 L/kg/day.

4.2.2 Daily Dose of Perchlorate

By combining the information on the concentration of perchlorate in drinking water from UCMR 1 and the specified drinking water intake rate, it is possible to estimate the daily dose of perchlorate being consumed at each PWS. This dose is estimated by the following equation:

$$D = \frac{DW_{ClO_4^-}}{DWI},$$

where:

D = dose of perchlorate (µg/kg/day)
$DW_{ClO_4^-}$ = the concentration of perchlorate in drinking water in µg/L
DWI = the bodyweight-adjusted drinking water intake rate in L/kg/day.

This dose is calculated based on both the pre- and post-rule concentration of perchlorate in drinking water.

4.2.3 Population Impacted

The population impacted by the rule for which benefits can be quantified is specific to live births from mothers who were served by a PWS with perchlorate concentrations at or above the potential MCLs. To determine the nationwide population of children that will experience a quantifiable benefit of avoided IQ decrements from reducing maternal perchlorate exposure during pregnancy, the EPA first estimated the total population being served by systems at or above the MCL based on data from UCMR 1. The EPA then multiplied the total population served for each effected PWS by the proportion of women of childbearing age (aged 15–44) in the United States, which is 19.7 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0Is16I8T","properties":{"formattedCitation":"(U.S. Census Bureau, 2017b)","plainCitation":"(U.S. Census Bureau, 2017b)","noteIndex":0},"citationItems":[{"id":945,"uris":["http://zotero.org/groups/945096/item

s/ZM7S6H44"],"uri":["http://zotero.org/groups/945096/items/ZM7S6H44"],"itemData":{"id":945,"type":"article","title":"Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2016.","URL":"https://www.census.gov/data/datasets/2016/demo/popest/nation-detail.html#ds","author":[{"literal":"U.S. Census Bureau"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The number of women of child-bearing age for each PWS was then multiplied by the annual number of live births in the United States, or 62 births per 1,000 women (6.2 percent) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"oSRGsU5q","properties":{"formattedCitation":"(Martin et al., 2017)","plainCitation":"(Martin et al., 2017)","noteIndex":0},"citationItems":[{"id":186,"uris":["http://zotero.org/groups/945096/items/MY6LPDKD"],"uri":["http://zotero.org/groups/945096/items/MY6LPDKD"],"itemData":{"id":186,"type":"article","title":"Births in the United States, 2016. NCHS Data Brief No. 287","URL":"https://www.cdc.gov/nchs/data/databriefs/db287.pdf","author":[{"family":"Martin","given":"J.A."},{"family":"Hamilton","given":"B.E."},{"family":"Osterman","given":"M.J.K"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The resulting impacted population characterized for the monetized benefits is summarized in [REF _Ref522698332 \h].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Size of the Total U.S. Population, Women of Child-Bearing Age and Live Births Exposed at or above the Potential MCLs to Perchlorate in Drinking Water

Potential MCL (µg/L)	Total U.S. Population		
	Total at or above MCL (A)	Women of Child-Bearing Age at or above the MCL (B = A x 19.7%)	Annual Live Births Occurring at or above the MCL (C = B x 6.2%)
56	32,432	6,385	396
18 (UCMR 1)	620,560	122,168	7,574
18 (national)[a]	659,547	129,843	8,050

a. EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is 1 of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the 6 UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA assumed that this population would incur benefits equivalent to the sampled entry point's population.

These resulting populations were then further divided into the proportion of live births born to women of each level of iodine intake, given that the dose-response relationship between perchlorate and altered maternal fT4 is dependent on the level of daily iodine intake (see Section [REF _Ref522534193 \r \h * MERGEFORMAT]).

The EPA estimated the distribution of iodine intakes of non-pregnant women of childbearing age (20–44) using data from NHANES 2011–2014 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"JsLCoBF1","properties":{"formattedCitation":"(CDC and NCHS, 2011; 2013)","plainCitation":"(CDC and NCHS, 2011;

2013)","noteIndex":0},"citationItems":[{"id":261,"uris":["http://zotero.org/groups/945096/items/G49EFPQ4"],"uri":["http://zotero.org/groups/945096/items/G49EFPQ4"],"itemData":{"id":261,"type":"report","title":"National Health and Nutrition Examination Survey Data","publisher":"U.S. Department of Health and Human Services, Centers for Disease Control and Prevention","publisher-place":"Hyattsville, MD","event-place":"Hyattsville, MD","URL":"https://wwwn.cdc.gov/nchs/nhanes/Search/Nhanes11_12.aspx","author":[{"literal":"CDC"},{"literal":"NCHS"}],"issued":{"date-parts":[["2011"]],"season":"2012"}}},{"id":"5Cn20MPv/ji5wASja","uris":["http://zotero.org/groups/635290/items/H5BG78PS"],"uri":["http://zotero.org/groups/635290/items/H5BG78PS"],"itemData":{"id":1260,"type":"report","title":"National Health and Nutrition Examination Survey Data","publisher":"U.S. Department of Health and Human Services, Centers for Disease Control and Prevention","publisher-place":"Hyattsville, MD","event-place":"Hyattsville, MD","URL":"https://wwwn.cdc.gov/nchs/nhanes/Search/Nhanes13_14.aspx","author":[{"literal":"CDC"},{"literal":"NCHS"}],"issued":{"date-parts":[["2013"]],"season":"2014"}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This was accomplished by first taking each participant's urinary iodine sample concentration from the NHANES and implementing the data smoothing technique outlined in Pleil and Sobus [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8Adyiuja","properties":{"formattedCitation":"(2016)","plainCitation":"(2016)","noteIndex":0},"citationItems":[{"id":269,"uris":["http://zotero.org/groups/945096/items/W6ZWA4ES"],"uri":["http://zotero.org/groups/945096/items/W6ZWA4ES"],"itemData":{"id":269,"type":"article-journal","title":"Estimating central tendency from a single spot measure: A closed-form solution for lognormally distributed biomarker data for risk assessment at the individual level","container-title":"Journal of Toxicology and Environmental Health, Part A","page":"837-847","volume":"79","issue":"18","source":"CrossRef","DOI":"10.1080/15287394.2016.1193108","ISSN":"1528-7394, 1087-2620","shortTitle":"Estimating central tendency from a single spot measure","language":"en","author":[{"family":"Pleil","given":"Joachim D."},{"family":"Sobus","given":"Jon R."}],"issued":{"date-parts":[["2016",9,16]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This technique accounts for the relative representativeness of a single spot measurement of iodine by predicting an intra-individual geometric mean concentration for each participant. The EPA applied the average of the published intraclass correlation coefficients (ICCs) for urinary spot measurements of iodine from Amouzegar and Azizi [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"EXM8M7pr","properties":{"formattedCitation":"(2013)","plainCitation":"(2013)","noteIndex":0},"citationItems":[{"id":268,"uris":["http://zotero.org/groups/945096/items/4894G8UH"],"uri":["http://zotero.org/groups/945096/items/4894G8UH"],"itemData":{"id":268,"type":"article-journal","title":"Variations of urinary iodine during the first trimester of pregnancy in an iodine-replete area. Comparison with non-pregnant women","container-title":"Hormones","page":"111–18","volume":"12","issue":"1","source":"Google Scholar","author":[{"family":"Amouzegar","given":"Atieh"},{"family":"Azizi","given":"Fereidoun"}],"issued":{"date-parts":[["2013"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] as the basis for this smoothing technique. The EPA then multiplied each participant's predicted geometric mean urinary iodine concentration by their estimated daily urinary output based on their NHANES measured urinary output data. When urinary output data

were not available, each missing value was replaced with median urinary output, or 1.33 L/day. The EPA then estimated the proportion of the population of non-pregnant women of childbearing age that fell into each daily iodine intake rate category, as summarized in [REF _Ref522614353 \h].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Proportion of Population Based on Maternal Iodine Intake Status

Iodine Intake Range (µg/day) Used for Benefits Analysis	Proportion of the Population
0 to < 55	7.14%
55 to < 60	2.15%
60 to < 65	1.06%
65 to < 70	1.86%
70 to < 75	1.31%
75 to < 80	3.10%
80 to < 85	2.62%
85 to < 90	1.20%
90 to < 95	1.83%
95 to < 100	2.94%
100 to < 125	13.56%
125 to < 150	9.08%
150 to < 170	10.31%
170 to < 300	24.47%
≥ 300	17.36%

4.2.4 Dose-Response

The process of connecting maternal perchlorate exposure to offspring IQ decrements requires two steps. The first step relates perchlorate exposure with changes in maternal fT4, and the second step relates the changes in maternal fT4 from the pre- to post-rule to changes in offspring IQ. Each step is described more thoroughly in the subsequent sections.

4.2.4.1 Step 1: Perchlorate Exposure to Changes in Maternal fT4

The EPA developed a BBDR model to describe the impact of perchlorate exposure on maternal fT4 levels in early pregnancy [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"zdqBNCcO","properties":{"formattedCitation":"(USEPA, 2018e)","plainCitation":"(USEPA, 2018e)","noteIndex":0},"citationItems":[{"id":926,"uris":["http://zotero.org/groups/945096/items/ANBBTDKU"],"uri":["http://zotero.org/groups/945096/items/ANBBTDKU"],"itemData":{"id":926,"type":"report","title":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","shortTitle":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This model has two main components: (1) a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption,

distribution, metabolism, and excretion of these two anions; and (2) a pharmacodynamic (PD) model, which describes the combined effect of varying perchlorate and iodide blood concentrations on the thyroidal uptake of iodide and subsequent production of thyroid hormones, most significantly T4. The pharmacokinetic portion contains a physiological description (e.g., organ volumes, blood flows) and chemical-specific information (e.g., partition coefficients; volume of distribution; rate constants for transport, metabolism, and elimination) that enable a prediction of perchlorate and iodide internal concentration at the critical target [i.e., thyroidal NIS in association with a particular exposure scenario (route of exposure, age, dose level)]. This portion of the model is similar to other physiologically based pharmacokinetic (PBPK) models and for perchlorate is simplified by the absence of metabolism. The PD portion of the model uses this internal concentration to simulate how the chemical will act within a known mechanism of action to perturb host systems and lead to a toxic effect. Thus, BBDR modeling attempts to predict the internal dose of a chemical associated with a particular exposure scenario, and the perturbation this internal dose can have on host systems.[6]

The BBDR model predicts serum thyroid hormone levels at:

- Specific gestational weeks. The EPA data that connect maternal fT4 concentrations to offspring IQ have a mean week of fT4 collection of approximately 13 gestational weeks (GWs). Subsequently in this benefits analysis, GW 13 data from the BBDR model have been used.
- A specific TSH feedback loop strength. As the benefits of reducing perchlorate exposure may extend to the entire population exposed, the BBDR model was run with the TSH feedback loop adjusted to its median level.
- Specific levels of iodine intake. Given that the dose-response relationship between perchlorate and fT4 is dependent on daily iodine intake concentrations, the EPA derived dose-response relationships based on BBDR model output for 13 different levels of iodine intake spanning from 50 µg/day to 300 µg/day.

To derive the dose-response functions for each level of daily iodine intake, the EPA first converted each dose of perchlorate that was input into the BBDR model to its equivalent drinking water concentration using the defined drinking water intake rate (see Section [REF _Ref522698474 \n \h]). Then, the EPA estimated a linear regression function of perchlorate concentration in drinking water on maternal fT4. This was done in order to derive a function specific to each iodine intake group that could be used to estimate the benefits of reduced

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[6] For additional information on the BBDR model, refer to Chapter 3 and Appendix A in the *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ahcggbXk","properties":{"formattedCitation":"(EPA, 2018e)","plainCitation":"(EPA, 2018e)","noteIndex":6},"citationItems":[{"id":926,"uris":["http://zotero.org/groups/945096/items/ANBBTDKU"],"uri":["http://zotero.org/groups/945096/items/ANBBTDKU"],"itemData":{"id":926,"type":"report","title":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","shortTitle":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true,"prefix":"EPA,"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

exposure to perchlorate at any possible water concentration, as opposed to just the water concentrations input into the BBDR model. The R^2 values of each regression analysis were evaluated to confirm the fit of the linear functional relationship between perchlorate and fT4. In all instances the R^2 values were 0.98 or greater, confirming a reasonable predictive power for values in-between the original perchlorate doses input into the BBDR model. The high R^2 values also confirm the linearity of the relationship between fT4 and perchlorate for each iodine intake level in the dose-range evaluated (0 to 10 µg/kg/day).

The BBDR model can only be run at discrete iodine intake levels and, therefore, the results for a single value of iodine intake were assigned to a range of iodine intake values for the purposes of informing a benefits assessment. The functions relating perchlorate to fT4 are summarized in [REF _Ref522614369 \h]. The raw output from the BBDR model is presented in [REF _Ref523405532 \n \h].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Effect Estimates Relating Perchlorate in Drinking Water to Changes in fT4 Based on Analysis of BBDR Model Results

Iodine Intake Used for BBDR Model (µg/day)	Iodine Intake Range (µg/day) Used for Benefits Analysis	Intercept	β Relating Perchlorate in Drinking Water (µg/L) to fT4 (pmol/L)
50	0 to < 55	8.26	-0.0008
55	55 to < 60	8.46	-0.0009
60	60 to < 65	8.66	-0.0010
65	65 to < 70	8.85	-0.0011
70	70 to < 75	9.05	-0.0012
75	75 to < 80	9.25	-0.0013
80	80 to < 85	9.45	-0.0015
85	85 to < 90	9.66	-0.0016
90	90 to < 95	9.86	-0.0017
95	95 to < 100	10.04	-0.0017
100	100 to < 125	10.19	-0.0016
125	125 to < 150	10.41	-0.0004
150	150 to < 170	10.47	-0.0002
170	170 to < 300	10.50	-0.0001
300	≥ 300	10.57	-0.00003

Using the inputs in [REF _Ref522614369 \h], pre- and post-rule maternal fT4 values are estimated using the following equation:

$$fT4_{i,p} = \beta_i \times P_p + I_i ,$$

where:

$fT4_{i,p}$ = fT4 concentration for population p at iodine intake range i (in picomoles per litre, pmol/L)
β_i = β from [REF _Ref522614369 \h] for iodine intake range i
P_p = perchlorate concentration in drinking water for population p (µg/L)

I_i = intercept from [REF _Ref522614369 \h] for iodine intake range i.

4.2.4.2 Step 2: Maternal fT4 to Offspring IQ

Following the SAB's recommendation, the EPA conducted a literature review to evaluate the most rigorous study or studies to use that associated changes in maternal fT4 to changes in offspring IQ.[7] To identify studies that connected incremental changes in maternal T4 or fT4 to incremental changes in offspring neurodevelopment, the EPA assessed 71 epidemiological studies using a 4-step approach and also assessed the feasibility of conducting de novo analysis on available datasets. Ultimately, the EPA selected its own reanalysis of the Korevaar et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Chy7rAPY","properties":{"formattedCitation":"(2016)","plainCitation":"(2016)","noteIndex":0},"citationItems":[{"id":43,"uris":["http://zotero.org/groups/945096/items/B968J6XI"],"uri":["http://zotero.org/groups/945096/items/B968J6XI"],"itemData":{"id":43,"type":"article-journal","title":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study","container-title":"The Lancet Diabetes & Endocrinology","page":"35-43","volume":"4","issue":"1","source":"ScienceDirect","abstract":"SummaryBackground\nThyroid hormone is involved in the regulation of early brain development. Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology.\nMethods\nIn this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free

[7] This process, analysis, and justification of the ultimate selection is presented in Chapters 5 and 6 of the *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UnXosuZ9","properties":{"formattedCitation":"(EPA, 2018e)","plainCitation":"(EPA, 2018e)","noteIndex":7},"citationItems":[{"id":926,"uris":["http://zotero.org/groups/945096/items/ANBBTDKU"],"uri":["http://zotero.org/groups/945096/items/ANBBTDKU"],"itemData":{"id":926,"type":"report","title":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","shortTitle":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true,"prefix":"EPA,"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

thyroxine.\nFindings\nData for child IQ were available for 3839 mother–child pairs, and MRI scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid-stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).\nInterpretation\nBoth low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.\nFunding\nThe Netherlands Organisation for Health Research and Development (ZonMw) and the European Community's Seventh Framework Programme.","DOI":"10.1016/S2213-8587(15)00327-7","ISSN":"2213-8587","shortTitle":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood","journalAbbreviation":"The Lancet Diabetes & Endocrinology","author":[{"family":"Korevaar","given":"Tim I M"},{"family":"Muetzel","given":"Ryan"},{"family":"Medici","given":"Marco"},{"family":"Chaker","given":"Layal"},{"family":"Jaddoe","given":"Vincent W V"},{"family":"Rijke","given":"Yolanda B","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A P"},{"family":"Visser","given":"Theo J"},{"family":"White","given":"Tonya"},{"family":"Tiemeier","given":"Henning"},{"family":"Peeters","given":"Robin P"}],"issued":{"date-parts":[["2016",1]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] dataset to be the basis for the function relating maternal fT4 to offspring IQ. This selection was based on the large sample size of the analysis dataset compared to the other studies; the ability to control for an appropriate set of confounders; the feasibility of assessing the appropriate dose-response relationship; and the ability to develop a function that is specific to particular ranges of fT4, but span the entire distribution of possible fT4 levels.[8] Based on the EPA's reanalysis, the concentration-response function relating fT4 to IQ is as follows:

[8] See Chapter 6 of the *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"JlnOzgLX","properties":{"formattedCitation":"(USEPA, 2018e)","plainCitation":"(USEPA, 2018e)","noteIndex":8},"citationItems":[{"id":926,"uris":["http://zotero.org/groups/945096/items/ANBBTDKU"],"uri":["http://zotero.org/groups/945096/items/ANBBTDKU"],"itemData":{"id":926,"type":"report","title":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","shortTitle":"Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

When $fT4_1$ and $fT4_0$ are both less than or equal to 11.76 pmol/L[9]:

$$\Delta IQ = (\gamma \times \ln(fT4_1)) - (\gamma \times \ln(fT4_0)) ,$$

where:

γ = coefficient from the EPA reanalysis of Korevaar et al. (2016), or 17.26 (3.77, 30.75)
$fT4_1$ = maternal fT4 under the perchlorate rule option in drinking water scenario
$fT4_0$ = maternal fT4 under the baseline perchlorate concentration in drinking water scenario.

When the fT4 values exceed 11.76, it is assumed that no benefits will accrue. This is based on the fact that the function derived for fT4 levels between 11.76 and 18.94 [the 10th to 90th percentiles from the Korevaar et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CIzJ3rfd","properties":{"formattedCitation":"(2016)","plainCitation":"(2016)","noteIndex":0},"citationItems":[{"id":43,"uris":["http://zotero.org/groups/945096/items/B968J6XI"],"uri":["http://zotero.org/groups/945096/items/B968J6XI"],"itemData":{"id":43,"type":"article-journal","title":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study","container-title":"The Lancet Diabetes & Endocrinology","page":"35-43","volume":"4","issue":"1","source":"ScienceDirect","abstract":"SummaryBackground\nThyroid hormone is involved in the regulation of early brain development. Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology.\nMethods\nIn this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine.\nFindings\nData for child IQ were available for 3839 mother–child pairs, and MRI scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations,

[9] This fT4 value represents untransformed values of the ln(fT4) values at each knot of the spline. The values were obtained by calculating exp(ln(fT4)).

this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid-stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).\nInterpretation\nBoth low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.\nFunding\nThe Netherlands Organisation for Health Research and Development (ZonMw) and the European Community's Seventh Framework Programme.","DOI":"10.1016/S2213-8587(15)00327-7","ISSN":"2213-8587","shortTitle":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood","journalAbbreviation":"The Lancet Diabetes & Endocrinology","author":[{"family":"Korevaar","given":"Tim I M"},{"family":"Muetzel","given":"Ryan"},{"family":"Medici","given":"Marco"},{"family":"Chaker","given":"Layal"},{"family":"Jaddoe","given":"Vincent W V"},{"family":"Rijke","given":"Yolanda B","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A P"},{"family":"Visser","given":"Theo J"},{"family":"White","given":"Tonya"},{"family":"Tiemeier","given":"Henning"},{"family":"Peeters","given":"Robin P"}],"issued":{"date-parts":[["2016",1]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] dataset] does not demonstrate a statistically significant relationship between fT4 and IQ (p-values greater than 0.8). However, given that the BBDR model results estimate the median fT4 to be 10.7 pmol/L with adequate iodine (i.e., iodine intake = 170 µg/day), it is unlikely that any significant benefits based on this cutpoint will be missed.

Combining the fT4 equation in Step 1 of the dose-response function with the ΔIQ equation in Step 2 for each iodine intake range group yields the following full dose-response equation:

$$\Delta IQ = \sum_{i=1}^{15} \left(\left(\left(\gamma \times \ln\left(\left(\beta_i P_{1p} + I_i \right) \right) \right) - \left(\gamma \times \ln\left(\left(\beta_i P_{0p} + I_i \right) \right) \right) \right) * IProp \right),$$

where:

γ = coefficient from the EPA reanalysis of Korevaar et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"I3Kk2AXD","properties":{"formattedCitation":"(2016)","plainCitation":"(2016)","noteIndex":0},"citationItems":[{"id":43,"uris":["http://zotero.org/groups/945096/items/B968J6XI"],"uri":["http://zotero.org/groups/945096/items/B968J6XI"],"itemData":{"id":43,"type":"article-journal","title":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study","container-title":"The Lancet Diabetes & Endocrinology","page":"35-43","volume":"4","issue":"1","source":"ScienceDirect","abstract":"SummaryBackground\nThyroid hormone is involved in the regulation of early brain development.

Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology.\nMethods\nIn this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine.\nFindings\nData for child IQ were available for 3839 mother–child pairs, and MRI scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid-stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).\nInterpretation\nBoth low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.\nFunding\nThe Netherlands Organisation for Health Research and Development (ZonMw) and the European Community's Seventh Framework Programme.","DOI":"10.1016/S2213-8587(15)00327-7","ISSN":"2213-8587","shortTitle":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood","journalAbbreviation":"The Lancet Diabetes & Endocrinology","author":[{"family":"Korevaar","given":"Tim I M"},{"family":"Muetzel","given":"Ryan"},{"family":"Medici","given":"Marco"},{

"family":"Chaker","given":"Layal"},{"family":"Jaddoe","given":"Vincent W V"},{"family":"Rijke","given":"Yolanda B","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A P"},{"family":"Visser","given":"Theo J"},{"family":"White","given":"Tonya"},{"family":"Tiemeier","given":"Henning"},{"family":"Peeters","given":"Robin P"}],"issued":{"date-parts":[["2016",1]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], or 17.26 (3.77, 30.75)

β_i = β from [REF _Ref522614369 \h * MERGEFORMAT] for iodine intake range *i*

P_{1p} = perchlorate concentration in drinking water (µg/L) under the rule scenario for population *p*

P_{0p} = perchlorate concentration in drinking water (µg/L) under the baseline scenario for population *p*

I_i = intercept from [REF _Ref522614369 \h * MERGEFORMAT] for iodine intake range *i*

i = iodine intake range group

$IProp$ = proportion of population from [REF _Ref522614353 \h * MERGEFORMAT] in a particular iodine intake range.

4.2.5 Value of an IQ point

To determine the value of avoided IQ losses, the EPA used estimates of the change in a child's future expected lifetime earnings per one IQ point reduction. Based on methods developed by Salkever [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"isjNxsEc","properties":{"formattedCitation":"(1995)","plainCitation":"(1995)","noteIndex":0},"citationItems":[{"id":182,"uris":["http://zotero.org/groups/945096/items/PMXG4BGW"],"uri":["http://zotero.org/groups/945096/items/PMXG4BGW"],"itemData":{"id":182,"type":"article-journal","title":"Updated estimates of earnings benefits from reduced exposure of children to environmental lead","container-title":"Environmental Research","page":"1-6","volume":"70","issue":"1","source":"PubMed","abstract":"The recent and important study by Schwartz found that almost three-fourths of the benefits of reduced lead exposure in children are in the form of earnings gains (earnings losses avoided). New data on recent trends in returns to education and cognitive skills in the labor market suggest a need to revise this estimate upward. Based on an analysis of data from the National Longitudinal Survey of Youth, the present study estimates that an upward revision of at least 50% (or $2.5 billion per annual birth cohort) is indicated. The study also finds evidence that percentage earnings gains are considerably larger for females than for males.","DOI":"10.1006/enrs.1995.1038","ISSN":"0013-9351","note":"PMID: 8603652","journalAbbreviation":"Environ. Res.","language":"eng","author":[{"family":"Salkever","given":"D. S."}],"issued":{"date-parts":[["1995",7]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the EPA estimates that a one point change in IQ results in a 1.865 percent change in lifetime earnings for males and a 3.397 percent change in lifetime earnings for females. The EPA estimated lifetime earnings separately for males and females using average education enrollment and annual earnings from 10 American Community Survey (ACS) Public Use Microdata Sample (PUMS) single-year samples (2008 to 2017). Then, the EPA weighted the male and female lifetime earnings by the proportion of the adult

population that is male and female, based on life tables from the Social Security Administration (SSA) [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"P2VLrPmO","properties":{"formattedCitation":"(U.S. Census Bureau, 2017a)","plainCitation":"(U.S. Census Bureau, 2017a)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":951,"uris":["http://zotero.org/groups/945096/items/MRQCZ8P9"],"uri":["http://zotero.org/groups/945096/items/MRQCZ8P9"],"itemData":{"id":951,"type":"article","title":"American Community Survey","author":[{"literal":"U.S. Census Bureau"}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Additionally, the EPA adjusted the change in lifetime earnings to account for the decreased average length of education associated with an IQ decrement. Also based on the methods developed by Salkever (1995), the EPA estimated that a one IQ point reduction leads to an average reduction in schooling of 0.0811 years for males and 0.0916 years for females. To estimate the costs associated with the change in educational attainment, the EPA used ACS PUMS enrollment data to determine the level at which the change occurs (i.e. secondary school versus postsecondary school) together with data on educational costs from the Digest of Education Statistics (Snyder and Dillow, 2016). The EPA also adjusted the values to account for lost earnings during the additional educational enrollment.

The net monetized value of a one IQ point change is change in lifetime earnings, net of the change in educational costs and foregone earnings. See [REF _Ref514841528 \n \h] for a description of the methodology.

[REF _Ref522614422 \h] summarizes the net value of an IQ point. Estimates are presented in 2017 dollars and are discounted using both a 3 percent and a 7 percent discount rate. The original analysis of the discounted present value of lifetime income differentials associated with a one-point IQ loss [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"B1LFmv0q","properties":{"formattedCitation":"(USEPA, 2018h)","plainCitation":"(USEPA, 2018h)","noteIndex":0},"citationItems":[{"id":1009,"uris":["http://zotero.org/groups/945096/items/RGCVVY9K"],"uri":["http://zotero.org/groups/945096/items/RGCVVY9K"],"itemData":{"id":1009,"type":"article","title":"Economic Analysis of the Proposed Rule to Revise the TSCA Dust Lead Hazard Standards","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] was discounted to the third year of life to reflect a typical exposure age to lead in dust. For the proposed perchlorate rule, the EPA further discounted the present value of lifetime income differentials three additional years to align the benefits of reduced perchlorate exposure more closely with prenatal exposure. This adjustment does not affect the total value of an IQ point over a lifetime but rather reflects the present value at birth rather than at age three. These revised values are presented in the bolded row in [REF _Ref522614422 \h].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Average Effects of a One-Point Change in IQ on Earnings (2017$)

Estimate Parameter	Discount Rate	
	3%	7%
Present value of lifetime earnings	$884,342	$205,144
IQ value	$23,269	$5,398
Additional education costs and lost earnings	$1,592	$691
Net value of an IQ point (IQ value less additional education costs and lost earnings) discounted to the third year of life	$21,677	$4,707
Net value of an IQ point, discounted to birth	**$19,838**	**$3,842**

4.2.6 Summary of Benefits due to Avoided IQ Decrements

Following the approach laid out in [REF _Ref523393377 \h] and the inputs laid out in the preceding sections, the EPA estimates between 30 and 243 points of lost IQ will be avoided in the affected populations each year, after full implementation. The EPA estimated the value of these benefits over a 35-year analysis period and accounted for a phase-in of control technology in year 6 for large CWSs and year 9 for all other systems (see Section [REF _Ref523415193 \r \h * MERGEFORMAT]). As such, benefits begin to accrue in year 6.

The EPA calculated the present value of total benefits in each year of the analysis period and discounted benefits to year 1 using both a 3 percent and 7 percent discount rate. [REF _Ref523390582 \h * MERGEFORMAT] and [REF _Ref525891578 \h * MERGEFORMAT] summarize the results at MCLs of 56 µg/L and 18 µg/L, respectively.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Annualized Benefits of Avoided IQ Decrements at an MCL of 56 µg/L (millions 2017$)

	Annual Delta IQ[a]	Annual Benefits[b]	
		3% Discount	7% Discount
Upper	243	$3.79	$0.64
Central	136	$2.12	$0.36
Lower	30	$0.46	$0.08

a. Annual change in IQ points in affected population is after full implementation.
b. Annualized benefits are calculated over a 35-year period and account for a phase-in of benefits corresponding to compliance in year 6 for large CWSs and in year 9 for all other systems.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Annualized Benefits of Avoided IQ Decrements at an MCL of 18 µg/L (millions 2017$)

	Annual Delta IQ[a]		UCMR 1[c]		National[b,c]	
	UCMR 1	National[b]	3% Discount	7% Discount	3% Discount	7% Discount
Upper	442	447	$6.90	$1.16	$6.97	$1.17
Central	248	251	$3.87	$0.65	$3.91	$0.66
Lower	54	55	$0.85	$0.14	$0.85	$0.14

a. Annual change in IQ points in affected population is after full implementation.
b. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is 1 of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the 6 UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 774,780 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. The EPA assumed that this population would incur benefits equivalent to the sampled entry point's population.
c. Annualized benefits are calculated over a 35-year period and account for a phase-in of benefits corresponding to compliance in year 6 for large CWSs and in year 9 for all other systems.

4.2.7 Limitations to Benefits Assessment

The quantitative benefits analysis has several limitations. The primary limitation is that it includes only one health endpoint and, therefore, excludes benefits of avoiding other types of adverse health effects of perchlorate exposure. Section 4.3 provides a qualitative discussion of other health effects. Other limitations include the health risks based on maximum recorded concentration estimates do not account for the possibility of exposure to concentrations greater than or less than this maximum concentration assuming that:

- Baseline fT4 is equal to the median likely underestimates disease benefits as the logarithmic relationship between maternal fT4 and child IQ leads to larger relative changes in fT4 with increasing levels of perchlorate with lower levels of baseline fT4, and
- A median TSH feedback loop strength for the exposed population does not incorporate the variability in the feedback mechanism of the body's creation of TSH in response to decreasing fT4.

4.3 Non-Monetized Benefits of Reduced Perchlorate Exposure

The monetized benefits do not include several types of non-quantifiable benefits of reduced perchlorate exposure. These consist of other health effects associated with perchlorate due to its alteration of iodine and thyroid hormone levels (see Section [REF _Ref523470708 \r \h * MERGEFORMAT]), improved perception of water quality (see Section [REF _Ref325447503 \r \h * MERGEFORMAT]), and the possibility of reducing other contaminants if perchlorate is reduced (see Section [REF _Ref325447528 \r \h * MERGEFORMAT]).

4.3.1 Additional Neurological Endpoints Associated with Reduced Iodine and Altered Thyroid Hormones

Given the evidence that perchlorate can alter iodine uptake, evidence examining the impact of reduced or low iodine are relevant in understanding the potential impacts of perchlorate exposure. One such study, a review by Bleichrodt and Born [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CpSKIcOJ","properties":{"formattedCitation":"(1994)","plainCitation":"(1994)","noteIndex":0},"citationItems":[{"id":178,"uris":["http://zotero.org/groups/945096/items/DDKMKVDC"],"uri":["http://zotero.org/groups/945096/items/DDKMKVDC"],"itemData":{"id":178,"type":"chapter","title":"A metaanalysis of research on iodine and its relationship to cognitive development","container-title":"The Damaged Brain of Iodine Deficiency","publisher":"Cognizant Communication","publisher-place":"New York, NY","page":"195-200","event-place":"New York, NY","author":[{"family":"Bleichrodt","given":"N"},{"family":"Born","given":"M."}],"issued":{"date-parts":[["1994"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], looked at 18 studies of iodine deficiency and mental development. In a meta-analysis, the authors calculated an effective size of 0.90 for iodine deficiency on cognitive development, indicating the mean scores for the two groups (the iodine-deficient group and the non-iodine-deficient group) were 0.90 of a standard deviation apart, or 13.5 IQ points.

Further, many studies evaluate the relationship between hypothyroxinemia and altered neurodevelopmental outcomes. The body of literature evaluates different populations, at different ages for neurodevelopmental assessment, and at various cut points for fT4 to define hypothyroxinemia, and finds a significant difference in performance on global cognitive tests when comparing the offspring of hypothyroxinemic women to those of non-hypothyroxinemic women [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"HEa1BIKe","properties":{"formattedCitation":"(Costeira et al., 2011; Ghassabian et al., 2014; J\\uc0\\u250{}lvez et al., 2013; Korevaar et al., 2016; Li et al., 2010; Pop et al., 2003; 1999)","plainCitation":"(Costeira et al., 2011; Ghassabian et al., 2014; Júlvez et al., 2013; Korevaar et al., 2016; Li et al., 2010; Pop et al., 2003; 1999)","noteIndex":0},"citationItems":[{"id":230,"uris":["http://zotero.org/groups/945096/items/P5AYCR9S"],"uri":["http://zotero.org/groups/945096/items/P5AYCR9S"],"itemData":{"id":230,"type":"article-journal","title":"Psychomotor development of children from an iodine-deficient region","container-title":"Journal of Pediatrics","page":"447-453","volume":"159","issue":"3","DOI":"10.1016/j.jpeds.2011.02.034","ISSN":"ISSN 0022-3476 EISSN 1097-6833","language":"English","author":[{"family":"Costeira","given":"M. J."},{"family":"Oliveira","given":"P."},{"family":"Santos","given":"N. C."},{"family":"Ares","given":"S."},{"family":"Sáenz-Rico","given":"B."},{"family":"Escobar","given":"G. M.","non-dropping-particle":"de"},{"family":"Palha","given":"J. A."}],"issued":{"date-parts":[["2011"]]}}},{"id":391,"uris":["http://zotero.org/groups/945096/items/CZUXXSSN"],"uri":["http://zotero.org/groups/945096/items/CZUXXSSN"],"itemData":{"id":391,"type":"article-journal","title":"Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children","container-title":"Journal of Clinical Endocrinology and Metabolism","page":"2383-

2390","volume":"99","issue":"7","DOI":"10.1210/jc.2013-4281","author":[{"family":"Ghassabian","given":"A."},{"family":"Marroun","given":"H. E."},{"family":"Peeters","given":"R. P."},{"family":"Jaddoe","given":"V. W."},{"family":"Hofman","given":"A."},{"family":"Verhulst","given":"F. C."},{"family":"Tiemeier","given":"H."},{"family":"White","given":"T."}],"issued":{"date-parts":[["2014"]]}}},{"id":187,"uris":["http://zotero.org/groups/945096/items/GWRUQ6NN"],"uri":["http://zotero.org/groups/945096/items/GWRUQ6NN"],"itemData":{"id":187,"type":"article-journal","title":"Thyroxine levels during pregnancy in healthy women and early child neurodevelopment","container-title":"Epidemiology","page":"150-157","volume":"24","issue":"1","DOI":"10.1097/EDE.0b013e318276ccd3","shortTitle":"Thyroxine levels during pregnancy in healthy women and early child neurodevelopment","author":[{"family":"Júlvez","given":"J"},{"family":"Álvarez-Pedrerol","given":"M"},{"family":"Rebagliato","given":"M"},{"family":"Murcia","given":"M"},{"family":"Forns","given":"J"},{"family":"Garcia-Esteban","given":"R"},{"family":"Lertxundi","given":"N"},{"family":"Espada","given":"M"},{"family":"Tardón","given":"A"},{"family":"Galán","given":"I R"},{"family":"Sunyer","given":"J"}],"issued":{"date-parts":[["2013"]]}}},{"id":43,"uris":["http://zotero.org/groups/945096/items/B968J6XI"],"uri":["http://zotero.org/groups/945096/items/B968J6XI"],"itemData":{"id":43,"type":"article-journal","title":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study","container-title":"The Lancet Diabetes & Endocrinology","page":"35-43","volume":"4","issue":"1","source":"ScienceDirect","abstract":"SummaryBackground\nThyroid hormone is involved in the regulation of early brain development. Since the fetal thyroid gland is not fully functional until week 18–20 of pregnancy, neuronal migration and other crucial early stages of intrauterine brain development largely depend on the supply of maternal thyroid hormone. Current clinical practice mostly focuses on preventing the negative consequences of low thyroid hormone concentrations, but data from animal studies have shown that both low and high concentrations of thyroid hormone have negative effects on offspring brain development. We aimed to investigate the association of maternal thyroid function with child intelligence quotient (IQ) and brain morphology.\nMethods\nIn this population-based prospective cohort study, embedded within the Generation R Study (Rotterdam, Netherlands), we investigated the association of maternal thyroid function with child IQ (assessed by non-verbal intelligence tests) and brain morphology (assessed on brain MRI scans). Eligible women were those living in the study area at their delivery date, which had to be between April 1, 2002, and Jan 1, 2006. For this study, women with available serum samples who presented in early pregnancy (<18 weeks) were included. Data for maternal thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies (at weeks 9–18 of pregnancy), and child IQ (assessed at a median of 6·0 years of age [95% range 5·6–7·9 years]) or brain MRI scans (done at a median of 8·0 years of age [6·2–10·0]) were obtained. Analyses were adjusted for potential confounders including concentrations of human chorionic gonadotropin and child thyroid-stimulating hormone and free thyroxine.\nFindings\nData for child IQ were available for 3839 mother–child pairs, and MRI scans were available from 646 children. Maternal free thyroxine concentrations showed an inverted U-shaped association with child IQ (p=0·0044), child grey matter volume (p=0·0062), and cortex volume (p=0·0011). For both low and high maternal free thyroxine concentrations, this association corresponded to a 1·4–3·8 points reduction in mean child IQ. Maternal thyroid-

stimulating hormone was not associated with child IQ or brain morphology. All associations remained similar after the exclusion of women with overt hypothyroidism and overt hyperthyroidism, and after adjustment for concentrations of human chorionic gonadotropin, child thyroid-stimulating hormone and free thyroxine or thyroid peroxidase antibodies (continuous or positivity).\nInterpretation\nBoth low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ and lower grey matter and cortex volume. The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with subclinical hypothyroidism during pregnancy, might carry the potential risk of adverse child neurodevelopment outcomes when the aim of treatment is to achieve high-normal thyroid function test results.\nFunding\nThe Netherlands Organisation for Health Research and Development (ZonMw) and the European Community's Seventh Framework Programme.","DOI":"10.1016/S2213-8587(15)00327-7","ISSN":"2213-8587","shortTitle":"Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood","journalAbbreviation":"The Lancet Diabetes & Endocrinology","author":[{"family":"Korevaar","given":"Tim I M"},{"family":"Muetzel","given":"Ryan"},{"family":"Medici","given":"Marco"},{"family":"Chaker","given":"Layal"},{"family":"Jaddoe","given":"Vincent W V"},{"family":"Rijke","given":"Yolanda B","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A P"},{"family":"Visser","given":"Theo J"},{"family":"White","given":"Tonya"},{"family":"Tiemeier","given":"Henning"},{"family":"Peeters","given":"Robin P"}],"issued":{"date-parts":[["2016",1]]}}},{"id":366,"uris":["http://zotero.org/groups/945096/items/L3Y92VI4"],"uri":["http://zotero.org/groups/945096/items/L3Y92VI4"],"itemData":{"id":366,"type":"article-journal","title":"Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months","container-title":"Clinical Endocrinology","page":"825-829","volume":"72","DOI":"10.1111/j.1365-2265.2009.03743.x","author":[{"family":"Li","given":"Y."},{"family":"Shan","given":"Z."},{"family":"Teng","given":"W."},{"family":"Yu","given":"X."},{"family":"Li","given":"Y."},{"family":"Fan","given":"C."},{"family":"Teng","given":"X."},{"family":"Guo","given":"R."},{"family":"Wang","given":"H."},{"family":"Li","given":"J."},{"family":"Chen","given":"Y."},{"family":"Wang","given":"W."},{"family":"Chawinga","given":"M."},{"family":"Zhang","given":"L."},{"family":"Yang","given":"L."},{"family":"Zhao","given":"Y."},{"family":"Hua","given":"T."}],"issued":{"date-parts":[["2010"]]}}},{"id":198,"uris":["http://zotero.org/groups/945096/items/WKCD55DW"],"uri":["http://zotero.org/groups/945096/items/WKCD55DW"],"itemData":{"id":198,"type":"article-journal","title":"Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study","container-title":"Clinical Endocrinology","page":"282-288","volume":"59","issue":"3","source":"PubMed","abstract":"OBJECTIVE: To evaluate the impact of maternal hypothyroxinaemia during early gestation (fT4 below the lowest tenth percentile and TSH within the reference range: 0.15-2.0 mIU/l) on infant development, together with any subsequent changes in fT4 during gestation.\nDESIGN: A prospective 3-year follow-up study of pregnant women and their children up to the age of 2 years.\nMEASUREMENTS: Child development was assessed by means of the Bayley Scales of Infant Development in children of women with hypothyroxinaemia (fT4 below the tenth percentile at 12 weeks' gestation) at 12 weeks' gestation (cases), and in children of women with fT4 between the 50th and 90th percentiles at 12 weeks' gestation, matched for parity and gravidity (controls). Maternal

thyroid function (fT4 and TSH) was assessed at 12, 24 and 32 weeks' gestation. The mental and motor function of 63 cases and 62 controls was compared at the age of 1 year, and of 57 cases and 58 controls at the age of 2 years.\nRESULTS: Children of women with hypothyroxinaemia at 12 weeks' gestation had delayed mental and motor function compared to controls: 10 index points on the mental scale (95% CI: 4.5-15 points, P = 0.003) and eight on the motor scale at the age of 1 year (95% CI: 2.3-12.8 points, P = 0.02), as well as eight index points on the mental (95% CI: 4-12 points, P = 0.02), and 10 on the motor scale (95%CI: 6-16 points, P = 0.005) at the age of 2 years. Children of hypothyroxinaemic women in whom the fT4 concentration was increased at 24 and 32 weeks' gestation had similar scores to controls, while in the controls, the developmental scores were not influenced by further declines in maternal fT4 at 24 and 32 weeks' gestation.\nCONCLUSIONS: Maternal hypothyroxinaemia during early gestation is an independent determinant of a delay in infant neurodevelopment. However, when fT4 concentrations increase during pregnancy in women who are hypothyroxinaemic during early gestation, infant development appears not to be adversely affected.","ISSN":"0300-0664","note":"PMID: 12919150","shortTitle":"Maternal hypothyroxinaemia during early pregnancy and subsequent child development","journalAbbreviation":"Clin. Endocrinol. (Oxf)","language":"eng","author":[{"family":"Pop","given":"Victor J."},{"family":"Brouwers","given":"Evelien P."},{"family":"Vader","given":"Huib L."},{"family":"Vulsma","given":"Thomas"},{"family":"Baar","given":"Anneloes L.","non-dropping-particle":"van"},{"family":"Vijlder","given":"Jan J.","non-dropping-particle":"de"}],"issued":{"date-parts":[["2003",9]]}}},{"id":13,"uris":["http://zotero.org/groups/945096/items/VERVX5Q7"],"uri":["http://zotero.org/groups/945096/items/VERVX5Q7"],"itemData":{"id":13,"type":"article-journal","title":"Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy","container-title":"Clinical Endocrinology","page":"149-155","volume":"50","issue":"2","source":"PubMed","abstract":"BACKGROUND: Maternal thyroid function during early pregnancy is an important determinant of early fetal brain development because the fetal thyroid is unable to produce any T4 before 12-14 weeks' gestation. Overt maternal hypothyroidism as seen in severe iodine-deficient areas is associated with severely impaired neurological development of the offspring. At present, it is not known whether low free T4 (fT4) levels during pregnancy in healthy women from iodine sufficient areas may affect fetal neurodevelopment.\nMETHODS: Neurodevelopment was assessed at 10 months of age in a cohort of 220 healthy children, born after uncomplicated pregnancies and deliveries, using the Bayley Scales of Infant Development. Maternal TSH, fT4 and TPO antibody status were assessed at 12 and 32 weeks' gestation. Maternal gestational fT4 concentration was defined as an independent parameter for child development.\nRESULTS: Children of women with fT4 levels below the 5th (< 9.8 pmol/l, n = 11) and 10th (< 10.4 pmol/l, n = 22) percentiles at 12 weeks' gestation had significantly lower scores on the Bayley Psychomotor Developmental Index (PDI) scale at 10 months of age, compared to children of mothers with higher fT4 values (t test, mean difference: 14.1, 95% confidence interval (CI): 5.9-22 and 7.4, 95% CI: 1.1-13.9, respectively). At 32 weeks' gestation, no significant differences were found. In the group of women with the lowest 10th percentile fT4 concentrations at 12 weeks' gestation, a positive correlation was found between the mothers' fT4 concentration and children's PDI scores (linear regression, R: 0.46, P = 0.03). After correction for confounding variables, a fT4 concentration below the 10th percentile at 12 weeks' gestation was a significant

risk factor for impaired psychomotor development (RR): 5.8, 95% CI: 1.3-12.6).\nCONCLUSIONS: Low maternal plasma fT4 concentrations during early pregnancy may be an important risk factor for impaired infant development.","ISSN":"0300-0664","note":"PMID: 10396355","journalAbbreviation":"Clin. Endocrinol. (Oxf)","language":"eng","author":[{"family":"Pop","given":"Victor J."},{"family":"Kuijpens","given":"J. L."},{"family":"Baar","given":"A. L.","non-dropping-particle":"van"},{"family":"Verkerk","given":"G."},{"family":"Son","given":"M. M.","non-dropping-particle":"van"},{"family":"Vijlder","given":"J. J.","non-dropping-particle":"de"},{"family":"Vulsma","given":"T."},{"family":"Wiersinga","given":"W. M."},{"family":"Drexhage","given":"H. A."},{"family":"Vader","given":"H. L."}],"issued":{"date-parts":[["1999",2]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. These findings are supported by several systematic reviews and/or meta-analyses including Fan and Wu [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rqZQc5Xy","properties":{"formattedCitation":"(2016)","plainCitation":"(2016)","noteIndex":0},"citationItems":[{"id":223,"uris":["http://zotero.org/groups/945096/items/ZEI2FPD9"],"uri":["http://zotero.org/groups/945096/items/ZEI2FPD9"],"itemData":{"id":223,"type":"article-journal","title":"The impact of thyroid abnormalities during pregnancy on subsequent neuropsychological development of the offspring: a meta-analysis","container-title":"The Journal of Maternal-Fetal & Neonatal Medicine","page":"3971-3976","volume":"29","issue":"24","source":"Taylor and Francis+NEJM","abstract":"Objective: To investigate the relationship between specific thyroid abnormalities in women during pregnancy and the subsequent neuropsychological development of their offspring.Methods: A systematic literature search of PubMed, Embase and Web of Science was conducted. Eligible studies were case-control or cohort study that explored this association with euthyroid thyroid abnormalities during pregnancy. The outcomes included intelligence scores and motor scores. Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated and heterogeneity was assessed with Cochrane Q chi-square test and I2 statistics. A fixed-effects or random-effects model was used to pool the estimates according to the heterogeneity among the included studies.Results: Six studies, involving 4449 participants, were included. Children of women with thyroid abnormalities had mean intelligence score of 6.27 points and motor score of 5.99 points lower than that of children of euthyroid women. Subgroup analysis suggested that, children of women with hypothyroxinaemia, subclinical hypothyroidism and positive TPOAb had mean intelligence scores of 5.69 points, 8.76 points and 10.55 points, and mean motor scores of 4.19 points, 9.98 points and 9.03 points lower than those of the controls, respectively.Conclusions: The thyroid abnormalities in pregnant women may adversely affect neuropsychological development of their offspring.","DOI":"10.3109/14767058.2016.1152248","ISSN":"1476-7058","note":"PMID: 26988121","shortTitle":"The impact of thyroid abnormalities during pregnancy on subsequent neuropsychological development of the offspring","author":[{"family":"Fan","given":"Xuegang"},{"family":"Wu","given":"Lina"}],"issued":{"date-parts":[["2016",12,16]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], Wang et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"zOjOR7X4","properties":{"formattedCitation":"(2016)","plainCitation":"(2016)","noteIndex":0},"citationItems":[{"id":238,"uris":["http://zotero.org/groups/945096/items/9HG6

HZ9G"],"uri":["http://zotero.org/groups/945096/items/9HG6HZ9G"],"itemData":{"id":238,"type":"article-journal","title":"Maternal thyroxine levels during pregnancy and outcomes of cognitive development in children","container-title":"Molecular Neurobiology","page":"2241-2248","volume":"53","issue":"4","source":"link.springer.com","abstract":"Though there were many studies assessing the relationship between maternal thyroxine levels during pregnancy and cognitive development in children, there was still lack of evidence for the association from a comprehensive assessment of published data. To get a more comprehensive estimate of the influence of low maternal thyroxine levels on cognitive function, a meta-analysis of prospective cohort studies was performed. Two electronic databases, MEDLINE and EMBASE, were searched for relevant prospective cohort studies. Relative risks (RR) with 95 % confidence intervals (95 % CI) were pooled using random-effect model of meta-analysis to assess the risk of delayed cognitive development in children. Seven prospective cohort studies with a total of 8273 mother-child pairs were included into the meta-analysis. There was obvious between-study heterogeneity in the meta-analysis (I2 = 69.6 %). Meta-analysis of using random-effect model showed that low maternal thyroxine level was significantly associated with a threefold risk of delayed cognitive development in children (random RR = 3.08, 95 % CI 1.83–5.18, P < 0.001). When excluding the study with largest weight, there was no obvious between-study heterogeneity in the left studies (I2 = 47.6 %), and meta-analysis using random-effect model showed that low maternal thyroxine level was still significantly associated with increased risk of delayed cognitive development in children (random RR = 3.76, 95 % CI 2.14–6.58, P < 0.001). Sensitivity analysis by omitting other studies by turns showed that there was no obvious change in the pooled risk estimates, and all pooled RRs were statistically significant. Therefore, the findings from the meta-analysis provide strong evidence for the association between maternal thyroxine levels during pregnancy and cognitive development in children. Low maternal thyroxine level is significantly associated with a threefold risk of delayed cognitive development in children.","DOI":"10.1007/s12035-015-9189-z","ISSN":"0893-7648, 1559-1182","journalAbbreviation":"Mol Neurobiol","language":"en","author":[{"family":"Wang","given":"Pingping"},{"family":"Gao","given":"Jian"},{"family":"Zhao","given":"Shihua"},{"family":"Guo","given":"Yong"},{"family":"Wang","given":"Zengfang"},{"family":"Qi","given":"Feng"}],"issued":{"date-parts":[["2016",5,1]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and Thompson et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NZdgQeGs","properties":{"formattedCitation":"(2018)","plainCitation":"(2018)","noteIndex":0},"citationItems":[{"id":75,"uris":["http://zotero.org/groups/945096/items/BSE4P6V3"],"uri":["http://zotero.org/groups/945096/items/BSE4P6V3"],"itemData":{"id":75,"type":"article-journal","title":"Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis","container-title":"Clinical Endocrinology","ISSN":"1365-2265","author":[{"family":"Thompson","given":"William"},{"family":"Russell","given":"Ginny"},{"family":"Baragwanath","given":"Genevieve"},{"family":"Matthews","given":"Justin"},{"family":"Vaidya","given":"Bijay"},{"family":"Thompson-Coon","given":"Jo"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Fan and Wu [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"9kq4N49p","properties":{"formattedCitation":"(2016)","plainCitation":"(2016)","

noteIndex":0},"citationItems":[{"id":223,"uris":["http://zotero.org/groups/945096/items/ZEI2FPD9"],"uri":["http://zotero.org/groups/945096/items/ZEI2FPD9"],"itemData":{"id":223,"type":"article-journal","title":"The impact of thyroid abnormalities during pregnancy on subsequent neuropsychological development of the offspring: a meta-analysis","container-title":"The Journal of Maternal-Fetal & Neonatal Medicine","page":"3971-3976","volume":"29","issue":"24","source":"Taylor and Francis+NEJM","abstract":"Objective: To investigate the relationship between specific thyroid abnormalities in women during pregnancy and the subsequent neuropsychological development of their offspring.Methods: A systematic literature search of PubMed, Embase and Web of Science was conducted. Eligible studies were case-control or cohort study that explored this association with euthyroid thyroid abnormalities during pregnancy. The outcomes included intelligence scores and motor scores. Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated and heterogeneity was assessed with Cochrane Q chi-square test and I2 statistics. A fixed-effects or random-effects model was used to pool the estimates according to the heterogeneity among the included studies.Results: Six studies, involving 4449 participants, were included. Children of women with thyroid abnormalities had mean intelligence score of 6.27 points and motor score of 5.99 points lower than that of children of euthyroid women. Subgroup analysis suggested that, children of women with hypothyroxinaemia, subclinical hypothyroidism and positive TPOAb had mean intelligence scores of 5.69 points, 8.76 points and 10.55 points, and mean motor scores of 4.19 points, 9.98 points and 9.03 points lower than those of the controls, respectively.Conclusions: The thyroid abnormalities in pregnant women may adversely affect neuropsychological development of their offspring.","DOI":"10.3109/14767058.2016.1152248","ISSN":"1476-7058","note":"PMID: 26988121","shortTitle":"The impact of thyroid abnormalities during pregnancy on subsequent neuropsychological development of the offspring","author":[{"family":"Fan","given":"Xuegang"},{"family":"Wu","given":"Lina"}],"issued":{"date-parts":[["2016",12,16]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and Wang et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"9Ku61OVo","properties":{"formattedCitation":"(2016)","plainCitation":"(2016)","noteIndex":0},"citationItems":[{"id":238,"uris":["http://zotero.org/groups/945096/items/9HG6HZ9G"],"uri":["http://zotero.org/groups/945096/items/9HG6HZ9G"],"itemData":{"id":238,"type":"article-journal","title":"Maternal thyroxine levels during pregnancy and outcomes of cognitive development in children","container-title":"Molecular Neurobiology","page":"2241-2248","volume":"53","issue":"4","source":"link.springer.com","abstract":"Though there were many studies assessing the relationship between maternal thyroxine levels during pregnancy and cognitive development in children, there was still lack of evidence for the association from a comprehensive assessment of published data. To get a more comprehensive estimate of the influence of low maternal thyroxine levels on cognitive function, a meta-analysis of prospective cohort studies was performed. Two electronic databases, MEDLINE and EMBASE, were searched for relevant prospective cohort studies. Relative risks (RR) with 95 % confidence intervals (95 % CI) were pooled using random-effect model of meta-analysis to assess the risk of delayed cognitive development in children. Seven prospective cohort studies with a total of 8273 mother-child pairs were included into the meta-analysis. There was obvious between-study heterogeneity in the meta-analysis (I2 = 69.6 %). Meta-analysis of using random-effect model showed that low maternal thyroxine level was significantly associated with a threefold risk of

delayed cognitive development in children (random RR = 3.08, 95 % CI 1.83–5.18, P < 0.001). When excluding the study with largest weight, there was no obvious between-study heterogeneity in the left studies (I2 = 47.6 %), and meta-analysis using random-effect model showed that low maternal thyroxine level was still significantly associated with increased risk of delayed cognitive development in children (random RR = 3.76, 95 % CI 2.14–6.58, P < 0.001). Sensitivity analysis by omitting other studies by turns showed that there was no obvious change in the pooled risk estimates, and all pooled RRs were statistically significant. Therefore, the findings from the meta-analysis provide strong evidence for the association between maternal thyroxine levels during pregnancy and cognitive development in children. Low maternal thyroxine level is significantly associated with a threefold risk of delayed cognitive development in children.","DOI":"10.1007/s12035-015-9189-z","ISSN":"0893-7648, 1559-1182","journalAbbreviation":"Mol Neurobiol","language":"en","author":[{"family":"Wang","given":"Pingping"},{"family":"Gao","given":"Jian"},{"family":"Zhao","given":"Shihua"},{"family":"Guo","given":"Yong"},{"family":"Wang","given":"Zengfang"},{"family":"Qi","given":"Feng"}],"issued":{"date-parts":[["2016",5,1]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] found that hypothyroxinemia was associated with a 5.7 point lower score on intelligence tests and a three-fold increased risk of delayed cognitive development in children, respectively. Thompson et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"0sv6dCVb","properties":{"formattedCitation":"(2018)","plainCitation":"(2018)","noteIndex":0},"citationItems":[{"id":75,"uris":["http://zotero.org/groups/945096/items/BSE4P6V3"],"uri":["http://zotero.org/groups/945096/items/BSE4P6V3"],"itemData":{"id":75,"type":"article-journal","title":"Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis","container-title":"Clinical Endocrinology","ISSN":"1365-2265","author":[{"family":"Thompson","given":"William"},{"family":"Russell","given":"Ginny"},{"family":"Baragwanath","given":"Genevieve"},{"family":"Matthews","given":"Justin"},{"family":"Vaidya","given":"Bijay"},{"family":"Thompson-Coon","given":"Jo"}],"issued":{"date-parts":[["2018"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] found maternal hypothyroxinemia to be associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests; but they did not find this association with attention-deficit/hyperactivity disorder (ADHD) or autism.

Additionally, studies have related maternal hypothyroxinemia with a plethora of other outcomes, including offspring's increased risk of schizophrenia [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UZtr4rms","properties":{"formattedCitation":"(Gyllenberg et al., 2016)","plainCitation":"(Gyllenberg et al., 2016)","noteIndex":0},"citationItems":[{"id":24,"uris":["http://zotero.org/groups/945096/items/937P2NGT"],"uri":["http://zotero.org/groups/945096/items/937P2NGT"],"itemData":{"id":24,"type":"article-journal","title":"Hypothyroxinemia during gestation and offspring schizophrenia in a national birth cohort","container-title":"Biological Psychiatry","page":"962-970","volume":"79","issue":"12","source":"PubMed","abstract":"BACKGROUND: Evidence from animal and human studies indicates that thyroid hormone deficiency during early gestation alters brain development. As schizophrenia is associated with prenatal brain insults and premorbid cognitive deficits, we tested the a priori hypothesis that serologically defined maternal

thyroid deficiency during early gestation to mid-gestation is associated with schizophrenia in offspring.\nMETHODS: The investigation is based on the Finnish Prenatal Study of Schizophrenia, a nested case-control study that included archived maternal sera from virtually all pregnancies since 1983 (N = >1 million). We identified all offspring in the cohort with a diagnosis of schizophrenia based on the national inpatient and outpatient register and matched them on sex, date of birth, and residence in Finland at time of onset of the case to comparison subjects (1:1) from the cohort. Maternal sera of 1010 case-control pairs were assessed for free thyroxine, and sera of 948 case-control pairs were assessed for thyroid-stimulating hormone.\nRESULTS: Maternal hypothyroxinemia (free thyroxine ≤10th percentile, normal thyroid-stimulating hormone) was associated with an increased odds of schizophrenia (odds ratio = 1.75, 95% confidence interval = 1.22-2.50, p = .002). When adjusted for maternal psychiatric history, province of birth, and maternal smoking during pregnancy, the association remained significant (odds ratio = 1.70, 95% confidence interval = 1.13-2.55, p = .010).\nCONCLUSIONS: In a large, national birth cohort, prospectively documented hypothyroxinemia during early gestation to mid-gestation was associated with increased odds of schizophrenia in offspring. This information can inform translational studies of maternal hypothyroxinemia examining molecular and cellular deviations relevant to schizophrenia.","DOI":"10.1016/j.biopsych.2015.06.014","ISSN":"1873-2402","note":"PMID: 26194598\nPMCID: PMC4684794","journalAbbreviation":"Biol. Psychiatry","language":"eng","author":[{"family":"Gyllenberg","given":"David"},{"family":"Sourander","given":"Andre"},{"family":"Surcel","given":"Heljä-Marja"},{"family":"Hinkka-Yli-Salomäki","given":"Susanna"},{"family":"McKeague","given":"Ian W."},{"family":"Brown","given":"Alan S."}],"issued":{"date-parts":[["2016",6,15]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], ADHD [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aNEaI0ec","properties":{"formattedCitation":"(Modesto et al., 2015)","plainCitation":"(Modesto et al., 2015)","noteIndex":0},"citationItems":[{"id":242,"uris":["http://zotero.org/groups/945096/items/K4FG7Q2X"],"uri":["http://zotero.org/groups/945096/items/K4FG7Q2X"],"itemData":{"id":242,"type":"article-journal","title":"Maternal mild thyroid hormone insufficiency in early pregnancy and attention-deficit/hyperactivity disorder symptoms in children","container-title":"JAMA pediatrics","page":"838-845","volume":"169","issue":"9","source":"PubMed","abstract":"IMPORTANCE: Maternal thyroid hormone insufficiency during pregnancy can affect children's cognitive development. Nevertheless, the behavioral outcomes of children exposed prenatally to mild thyroid hormone insufficiency are understudied.\nOBJECTIVE: To examine whether exposure to maternal mild thyroid hormone insufficiency in early pregnancy was related to symptoms of attention-deficit/hyperactivity disorder (ADHD) in children at 8 years of age.\nDESIGN, SETTING, AND PARTICIPANTS: The study was embedded within the Generation R, a population-based birth cohort in the Netherlands. Children in the Generation R Study are followed up from birth (April 1, 2002, through January 31, 2006) until young adulthood. Of the 4997 eligible mother-child pairs with data on maternal thyroid levels (excluding twins), 3873 pairs of children and caregivers (77.5%) visited the Generation R research center for in-depth assessments and were included in the main analyses. Data collection in Generation R started December 1, 2001 (enrollment of pregnant women), and is ongoing. For this study, we used the data that were collected until January 1, 2014. Data analyses started on January 31 and finished June 30,

2014.\nMAIN OUTCOMES AND MEASURES: Maternal hypothyroxinemia, characterized by low levels of free thyroxine coexisting with reference thyrotropin levels, and children's symptoms of ADHD. Maternal thyroid hormone levels (thyrotropin, free thyroxine, thyroid peroxidase antibodies) were measured at a mean (SD) of 13.6 (1.9) weeks of gestation. Children's ADHD symptoms were assessed at 8 years of age using the Conners' Parent Rating Scale-Revised Short Form; higher scores indicate more ADHD symptoms (possible range, 0-36).\nRESULTS: Maternal hypothyroxinemia (n = 127) in early pregnancy was associated with higher scores for ADHD symptoms in children at 8 years of age after adjustments for child and maternal factors (ie, sex, ethnicity, maternal age, maternal educational level, and income) (increase in ADHD scores, 7% [95% CI, 0.3%-15%]). The results remained essentially unchanged when women with elevated levels of thyroid peroxidase antibodies were excluded from the analyses (increase in ADHD scores, 8% [95% CI, 1%-16%]). Additional adjustment for children's IQ or comorbid autistic symptoms attenuated the association (increase in ADHD scores adjusted for autistic symptoms, 7% [95% CI, 1%-15%]; increase in ADHD scores adjusted for IQ, 6% [95% CI, 1%-14%]).\nCONCLUSIONS AND RELEVANCE: Children exposed to maternal hypothyroxinemia in early pregnancy had more ADHD symptoms, independent of confounders. This finding suggests that intrauterine exposure to insufficient thyroid hormone levels influences neurodevelopment in offspring.","DOI":"10.1001/jamapediatrics.2015.0498","ISSN":"2168-6211","note":"PMID: 26146876","journalAbbreviation":"JAMA Pediatr","language":"eng","author":[{"family":"Modesto","given":"Thiago"},{"family":"Tiemeier","given":"Henning"},{"family":"Peeters","given":"Robin P."},{"family":"Jaddoe","given":"Vincent W. V."},{"family":"Hofman","given":"Albert"},{"family":"Verhulst","given":"Frank C."},{"family":"Ghassabian","given":"Akhgar"}],"issued":{"date-parts":[["2015",9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], expressive language delay [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aYMgQU8N","properties":{"formattedCitation":"(Henrichs et al., 2010)","plainCitation":"(Henrichs et al., 2010)","noteIndex":0},"citationItems":[{"id":383,"uris":["http://zotero.org/groups/945096/items/NZRKVAQJ"],"uri":["http://zotero.org/groups/945096/items/NZRKVAQJ"],"itemData":{"id":383,"type":"article-journal","title":"Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study","container-title":"Journal of Clinical Endocrinology and Metabolism","page":"4227-4234","volume":"95","issue":"9","DOI":"10.1210/jc.2010-0415","author":[{"family":"Henrichs","given":"J."},{"family":"Bongers-Schokking","given":"J. J."},{"family":"Schenk","given":"J. J."},{"family":"Ghassabian","given":"A."},{"family":"Schmidt","given":"H. G."},{"family":"Visser","given":"T. J."},{"family":"Hooijkaas","given":"H."},{"family":"Muinck Keizer-Schrama","given":"S. M. P. F.","non-dropping-particle":"de"},{"family":"Hofman","given":"A."},{"family":"Jaddo","given":"V. V. W."},{"family":"Visser","given":"W."},{"family":"Steegers","given":"E. A. P."},{"family":"Verhulst","given":"F. C."},{"family":"Rijke","given":"Y. B.","non-dropping-particle":"de"},{"family":"Tiemeier","given":"H."}],"issued":{"date-

parts":[["2010"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], reduced school performance [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Kh6JBpyz","properties":{"formattedCitation":"(Noten et al., 2015)","plainCitation":"(Noten et al., 2015)","noteIndex":0},"citationItems":[{"id":10,"uris":["http://zotero.org/groups/945096/items/I9KUUQIF"],"uri":["http://zotero.org/groups/945096/items/I9KUUQIF"],"itemData":{"id":10,"type":"article-journal","title":"Maternal hypothyroxinaemia in early pregnancy and school performance in 5-year-old offspring","container-title":"European Journal of Endocrinology","page":"563-571","volume":"173","issue":"5","source":"PubMed","abstract":"OBJECTIVE: Overt hypothyroidism in pregnant women is associated with a lower intelligence quotient in their children. More recently, subtle decreases in maternal thyroid function have also been associated with neurodevelopmental impairment in offspring. We tested the effect of hypothyroxinaemia during early pregnancy on school performance.\nDESIGN: This was a longitudinal study that included the data of 1196 mother-child pairs from the Amsterdam Born Children and Their Development study.\nMETHODS: Maternal serum free thyroxine (T4) and TSH were obtained at a median gestational age of 12.9 (interquartile range: 11.9-14.3) weeks. School performance was assessed at age 5 years and based on scores obtained in arithmetic and language tests from the national monitoring and evaluation system. Poor school performance was defined as a test result <25th percentile and subnormal school performance as a result <50th percentile of the norm population. To estimate the impact of possible non-response bias, we conducted inverse-probability weighted analyses.\nRESULTS: Maternal hypothyroxinaemia (i.e., a maternal free T4 in the lowest 10% of distribution) was associated with a 1.61 (95% CI: 1.05-2.47) -fold increased odds of subnormal arithmetic performance after adjustment for confounders (P=0.03). However, the odds ratio dropped to 1.48 (95% CI: 0.94-2.32) after inverse-probability weighting (P=0.09). No such relations were found with TSH.\nCONCLUSIONS: Maternal hypothyroxinaemia at the end of the first trimester was associated with reduced performance in an arithmetic test, but not in a language test, in 5-year-old offspring. However, our results should be interpreted carefully because of possible non-response bias.","DOI":"10.1530/EJE-15-0397","ISSN":"1479-683X","note":"PMID: 26306579","journalAbbreviation":"Eur. J. Endocrinol.","language":"eng","author":[{"family":"Noten","given":"Anna M. E."},{"family":"Loomans","given":"Eva M."},{"family":"Vrijkotte","given":"Tanja G. M."},{"family":"Ven","given":"Peter M.","non-dropping-particle":"van de"},{"family":"Trotsenburg","given":"A. S. Paul","non-dropping-particle":"van"},{"family":"Rotteveel","given":"Joost"},{"family":"Eijsden","given":"Manon","non-dropping-particle":"van"},{"family":"Finken","given":"Martijn J. J."}],"issued":{"date-parts":[["2015",11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], increased odds of autism [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"IWvGVIDk","properties":{"formattedCitation":"(Rom\\uc0\\u225{}n et al., 2013)","plainCitation":"(Román et al., 2013)","noteIndex":0},"citationItems":[{"id":94,"uris":["http://zotero.org/groups/945096/items/3W4UTVXX"],"uri":["http://zotero.org/groups/945096/items/3W4UTVXX"],"itemData":{"id":94,"type":"article-journal","title":"Association of gestational maternal hypothyroxinemia and increased autism risk","container-title":"Annals of Neurology","page":"733-

742","volume":"74","issue":"5","DOI":"10.1002/ana.23976","author":[{"family":"Román","given":"G. C."},{"family":"Ghassabian","given":"A."},{"family":"Bongers-Schokking","given":"J."},{"family":"Jaddoe","given":"V. W. V."},{"family":"Hofman","given":"A."},{"family":"Rijke","given":"Y. B.","non-dropping-particle":"de"},{"family":"Verhulst","given":"F. C."},{"family":"Tiemeier","given":"H."}],"issued":{"date-parts":[["2013"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and more [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"exydK8ZV","properties":{"formattedCitation":"(Finken et al., 2013; Kooistra et al., 2006; Noten et al., 2015; Oostenbroek et al., 2017; P\\uc0\\u228{}kkil\\uc0\\u228{} et al., 2015; van Mil et al., 2012)","plainCitation":"(Finken et al., 2013; Kooistra et al., 2006; Noten et al., 2015; Oostenbroek et al., 2017; Päkkilä et al., 2015; van Mil et al., 2012)","noteIndex":0},"citationItems":[{"id":8,"uris":["http://zotero.org/groups/945096/items/XFMWP565"],"uri":["http://zotero.org/groups/945096/items/XFMWP565"],"itemData":{"id":8,"type":"article-journal","title":"Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring","container-title":"The Journal of Clinical Endocrinology & Metabolism","page":"1417-1426","volume":"98","issue":"4","source":"CrossRef","DOI":"10.1210/jc.2012-3389","ISSN":"0021-972X, 1945-7197","language":"en","author":[{"family":"Finken","given":"Martijn J. J."},{"family":"Eijsden","given":"Manon","non-dropping-particle":"van"},{"family":"Loomans","given":"Eva M."},{"family":"Vrijkotte","given":"Tanja G. M."},{"family":"Rotteveel","given":"Joost"}],"issued":{"date-parts":[["2013",4]]}}},{"id":375,"uris":["http://zotero.org/groups/945096/items/SKGYQRVE"],"uri":["http://zotero.org/groups/945096/items/SKGYQRVE"],"itemData":{"id":375,"type":"article-journal","title":"Neonatal effects of maternal hypothyroxinemia during early pregnancy","container-title":"Pediatrics","page":"161-167","volume":"117","issue":"1","author":[{"family":"Kooistra","given":"L."},{"family":"Crawford","given":"S."},{"family":"Baar","given":"A. L.","non-dropping-particle":"van"},{"family":"Brouwers","given":"E."},{"family":"Pop","given":"V."}],"issued":{"date-parts":[["2006"]]}}},{"id":10,"uris":["http://zotero.org/groups/945096/items/I9KUUQIF"],"uri":["http://zotero.org/groups/945096/items/I9KUUQIF"],"itemData":{"id":10,"type":"article-journal","title":"Maternal hypothyroxinaemia in early pregnancy and school performance in 5-year-old offspring","container-title":"European Journal of Endocrinology","page":"563-571","volume":"173","issue":"5","source":"PubMed","abstract":"OBJECTIVE: Overt hypothyroidism in pregnant women is associated with a lower intelligence quotient in their children. More recently, subtle decreases in maternal thyroid function have also been associated with neurodevelopmental impairment in offspring. We tested the effect of hypothyroxinaemia during early pregnancy on school performance.\nDESIGN: This was a longitudinal study that included the data of 1196 mother-child pairs from the Amsterdam Born Children and Their Development study.\nMETHODS: Maternal serum free thyroxine (T4) and TSH were obtained at a median gestational age of 12.9 (interquartile range: 11.9-14.3) weeks. School performance was assessed at age 5 years and based on scores obtained in arithmetic and language tests from the national monitoring and evaluation system. Poor school performance was defined as a test

result <25th percentile and subnormal school performance as a result <50th percentile of the norm population. To estimate the impact of possible non-response bias, we conducted inverse-probability weighted analyses.\nRESULTS: Maternal hypothyroxinaemia (i.e., a maternal free T4 in the lowest 10% of distribution) was associated with a 1.61 (95% CI: 1.05-2.47) -fold increased odds of subnormal arithmetic performance after adjustment for confounders (P=0.03). However, the odds ratio dropped to 1.48 (95% CI: 0.94-2.32) after inverse-probability weighting (P=0.09). No such relations were found with TSH.\nCONCLUSIONS: Maternal hypothyroxinaemia at the end of the first trimester was associated with reduced performance in an arithmetic test, but not in a language test, in 5-year-old offspring. However, our results should be interpreted carefully because of possible non-response bias.","DOI":"10.1530/EJE-15-0397","ISSN":"1479-683X","note":"PMID: 26306579","journalAbbreviation":"Eur. J. Endocrinol.","language":"eng","author":[{"family":"Noten","given":"Anna M. E."},{"family":"Loomans","given":"Eva M."},{"family":"Vrijkotte","given":"Tanja G. M."},{"family":"Ven","given":"Peter M.","non-dropping-particle":"van de"},{"family":"Trotsenburg","given":"A. S. Paul","non-dropping-particle":"van"},{"family":"Rotteveel","given":"Joost"},{"family":"Eijsden","given":"Manon","non-dropping-particle":"van"},{"family":"Finken","given":"Martijn J. J."}],"issued":{"date-parts":[["2015",11]]}}},{"id":348,"uris":["http://zotero.org/groups/945096/items/2PNIXCER"],"uri":["http://zotero.org/groups/945096/items/2PNIXCER"],"itemData":{"id":348,"type":"article-journal","title":"Maternal hypothyroxinaemia in early pregnancy and problem behavior in 5-year-old offspring","container-title":"Psychoneuroendocrinology","page":"29-35","volume":"81","author":[{"family":"Oostenbroek","given":"M. H. W."},{"family":"Kersten","given":"R. H. J."},{"family":"Tros","given":"B."},{"family":"Kunst","given":"A. E."},{"family":"Vrijkotte","given":"T. G. M."},{"family":"Finken","given":"M. J. J."}],"issued":{"date-parts":[["2017"]]}}},{"id":344,"uris":["http://zotero.org/groups/945096/items/6ZHERLXP"],"uri":["http://zotero.org/groups/945096/items/6ZHERLXP"],"itemData":{"id":344,"type":"article-journal","title":"Maternal and Child's Thyroid Function and Child's Intellect and Scholastic Performance","container-title":"Thyroid","page":"1363-1374","volume":"25","issue":"12","DOI":"10.1787/9789264091450-e","author":[{"family":"Päkkilä","given":"F."},{"family":"Männistö","given":"T."},{"family":"Hartikainen","given":"A.-L."},{"family":"Ruokonen","given":"A."},{"family":"et al","given":""}],"issued":{"date-parts":[["2015"]]}}},{"id":68,"uris":["http://zotero.org/groups/945096/items/ICMQPI5W"],"uri":["http://zotero.org/groups/945096/items/ICMQPI5W"],"itemData":{"id":68,"type":"article-journal","title":"Maternal hypothryoxinemia during pregnancy and growth of the fetal and infant head","container-title":"Reproductive Sciences","page":"1315-1322","volume":"19","issue":"12","DOI":"10.1177/1933719112450338","author":[{"family":"Mil","given":"N. H.","non-dropping-particle":"van"},{"family":"Steegers-Theunissen","given":"Regine P. M."},{"family":"Bongers-Schokking","given":"Jacoba J."},{"family":"El Marroun","given":"Hanan"},{"family":"Ghassabian","given":"Akhgar"},{"family":"Hofman","given":"Albert"},{"family":"Jaddoe","given":"Vincent W. V."},{"family":"Verhulst","given":"Frank C."},{"family":"Rijke","given":"Yolanda B.","non-dropping-particle":"de"},{"family":"Steegers","given":"Eric A.

P."},{"family":"Tiemeier","given":"Henning"}],"issued":{"date-parts":[["2012"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. These studies demonstrate the sensitivity of the offspring of hypothyroxinemic mothers to adverse neurodevelopmental effects. As such, it can be reasonably concluded that any compound that may reduce maternal fT4, such as perchlorate, can increase the odds of these adverse neurodevelopmental outcomes.

4.3.2 Thyroid Hormone Levels and CVD, and Conclusion on Benefits Analysis

Multiple studies have established an association between overt thyroid disorders and CVD risk [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"obr6ckXN","properties":{"formattedCitation":"(Becker, 1985; Boelaert and Franklyn, 2005; Vanhaelst et al., 1967)","plainCitation":"(Becker, 1985; Boelaert and Franklyn, 2005; Vanhaelst et al., 1967)","noteIndex":0},"citationItems":[{"id":175,"uris":["http://zotero.org/groups/945096/items/LBUYMCGB"],"uri":["http://zotero.org/groups/945096/items/LBUYMCGB"],"itemData":{"id":175,"type":"article-journal","title":"Hypothyroidism and atherosclerotic heart disease: pathogenesis, medical management, and the role of coronary artery bypass surgery","container-title":"Endocrine Reviews","page":"432-440","volume":"6","issue":"3","source":"PubMed","DOI":"10.1210/edrv-6-3-432","ISSN":"0163-769X","note":"PMID: 3896769","shortTitle":"Hypothyroidism and atherosclerotic heart disease","journalAbbreviation":"Endocr. Rev.","language":"eng","author":[{"family":"Becker","given":"C."}],"issued":{"date-parts":[["1985"]]}}},{"id":177,"uris":["http://zotero.org/groups/945096/items/VTEHRNNF"],"uri":["http://zotero.org/groups/945096/items/VTEHRNNF"],"itemData":{"id":177,"type":"article-journal","title":"Thyroid hormone in health and disease","container-title":"The Journal of Endocrinology","page":"1-15","volume":"187","issue":"1","source":"PubMed","abstract":"Thyroid disease is common, affecting around 2% of women and 0.2% of men in the UK. Our understanding of the effects of thyroid hormones under physiological circumstances, as well as in pathological conditions, has increased dramatically during the last two centuries and it has become clear that overt thyroid dysfunction is associated with significant morbidity and mortality. Both hypo-and hyperthyroidism and their treatments have been linked with increased risk from cardiovascular disease and the adverse effects of thyrotoxicosis in terms of osteoporosis risk are well established. Although the evidence suggests that successful treatment of overt thyroid dysfunction significantly improves overall survival, the issue of treating mild or subclinical hyper- and hypothyroidism remains controversial. Furthermore, the now well-established effects of thyroid hormones on neurodevelopment have sparked a whole new debate regarding the need to screen pregnant women for thyroid function abnormalities. This review describes the current evidence of the effects of thyroid hormone on the cardiovascular, skeletal and neurological systems, as well as the influence of thyroid diseases and their treatments on the development of malignancy. Furthermore we will describe some recent developments in our understanding of the relationship between thyroid status and health.","DOI":"10.1677/joe.1.06131","ISSN":"0022-0795","note":"PMID: 16214936","journalAbbreviation":"J. Endocrinol.","language":"eng","author":[{"family":"Boelaert","given":"K."},{"family":"Franklyn","given":"J. A."}],"issued":{"date-parts":[["2005",10]]}}},{"id":176,"uris":["http://zotero.org/groups/945096/items/LWRY4IH9"],

"uri":["http://zotero.org/groups/945096/items/LWRY4IH9"],"itemData":{"id":176,"type":"article-journal","title":"Coronary-artery disease in hypothyroidism. Observations in clinical myxoedema","container-title":"Lancet (London, England)","page":"800-802","volume":"2","issue":"7520","source":"PubMed","ISSN":"0140-6736","note":"PMID: 4167274","journalAbbreviation":"Lancet","language":"eng","author":[{"family":"Vanhaelst","given":"L."},{"family":"Neve","given":"P."},{"family":"Chailly","given":"P."},{"family":"Bastenie","given":"P. A."}],"issued":{"date-parts":[["1967",10,14]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, Canaris et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"udg4xeBb","properties":{"formattedCitation":"(2000)","plainCitation":"(2000)","noteIndex":0},"citationItems":[{"id":418,"uris":["http://zotero.org/groups/945096/items/C3P4KCLI"],"uri":["http://zotero.org/groups/945096/items/C3P4KCLI"],"itemData":{"id":418,"type":"article-journal","title":"The Colorado Thyroid Disease Prevalence Study","container-title":"Arch Intern Med","page":"526-534","volume":"160","author":[{"family":"Canaris","given":"G. J."},{"family":"Manowitz","given":"N. R."},{"family":"Mayor","given":"G."},{"family":"Ridgway","given":"E. C."}],"issued":{"date-parts":[["2000"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] found that there are statistically significant trends when examining a person's TSH and T4 levels compared to total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Further, Asvold et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ggh7yLw1","properties":{"formattedCitation":"(2007)","plainCitation":"(2007)","noteIndex":0},"citationItems":[{"id":431,"uris":["http://zotero.org/groups/945096/items/LN473TQK"],"uri":["http://zotero.org/groups/945096/items/LN473TQK"],"itemData":{"id":431,"type":"article-journal","title":"The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT study","container-title":"European Journal of Endocrinology","page":"181-186","volume":"156","author":[{"family":"Asvold","given":"B."},{"family":"Vatten","given":"L. J."},{"family":"Nilsen","given":"T."},{"family":"Bjoro","given":"T."}],"issued":{"date-parts":[["2007"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] found that increases in TSH, even within the normal range, can increase an individual's risk of fatal coronary heart disease.

4.3.3 Reduction of Other Co-Occurring Contaminants

Many of the treatment techniques used to remove perchlorate from drinking water could also potentially remove nitrate, a co-occurring contaminant and a goitrogen.[10] In an analysis of California drinking water sources, perchlorate was found to co-occur with nitrate, although nitrate concentrations were also found to be significantly higher and to occur over a broader geographic area [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"dEZWePMn","properties":{"formattedCitation":"(Kimbrough and Parekh, 2007)","plainCitation":"(Kimbrough and Parekh,

[10] Goitrogens are substances that suppress the function of the [HYPERLINK "http://en.wikipedia.org/wiki/Thyroid" \o "Thyroid"] by interfering with [HYPERLINK "http://en.wikipedia.org/wiki/Iodine" \o "Iodine"] uptake, which can cause an enlargement of the thyroid (e.g., a goiter is a swelling of the thyroid).

2007)","noteIndex":0},"citationItems":[{"id":174,"uris":["http://zotero.org/groups/945096/items/68BUPB77"],"uri":["http://zotero.org/groups/945096/items/68BUPB77"],"itemData":{"id":174,"type":"article-journal","title":"Occurrence and co-occurrence of perchlorate and nitrate in California drinking water sources","container-title":"Journal (American Water Works Association)","page":"126-132","volume":"99","issue":"9","source":"JSTOR","ISSN":"0003-150X","author":[{"family":"Kimbrough","given":"D.E."},{"family":"Parekh","given":"P."}],"issued":{"date-parts":[["2007"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Additionally, in a study of 326 groundwater samples from "pristine" locations across the contiguous United States, a highly significant positive correlation was found between perchlorate and nitrate concentrations [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Hhrd7B9k","properties":{"formattedCitation":"(Parker et al., 2008)","plainCitation":"(Parker et al., 2008)","noteIndex":0},"citationItems":[{"id":173,"uris":["http://zotero.org/groups/945096/items/6D2GLW89"],"uri":["http://zotero.org/groups/945096/items/6D2GLW89"],"itemData":{"id":173,"type":"article-journal","title":"Perchlorate in groundwater: a synoptic survey of \"pristine\" sites in the coterminous United States","container-title":"Environmental Science & Technology","page":"1465-1471","volume":"42","issue":"5","source":"PubMed","abstract":"Perchlorate is widely used as an oxidant in solid rocket propellants and energetic applications, and it has frequently been detected in groundwaters at concentrations relevant to human health. The possibility of naturally occurring perchlorate has only recently received significant attention. Relying primarily on domestic, agricultural, and recreational wells, we utilized a network of volunteers to help collect 326 groundwater samples from across the coterminous United States. Care was taken to avoid known, USEPA-documented sites of perchlorate use or release, as well as perchlorate contamination due to disinfection using hypochlorite. Using IC-ESI-MS and a Cl18O4- internal standard, we achieved a method detection limit (MDL) of 40 ng/L perchlorate and a minimum reporting level (MRL) of 120 ng/L. Of the 326 samples, 147 (45%) were below the MDL, while 42 (13%) were between the MDL and the MRL. Of the 137 samples that could be quantified, most (109) contained < 1000 ng/L perchlorate; the remaining 28 samples contained from 1000 to 10400 ng/L. Our results support the notion that perchlorate occurs naturally in many groundwaters, but the unusually high concentrations (> 10000 ng/L) previously reported for the west-central Texas area appear to be anomalous. Perchlorate concentrations were positively correlated with nitrate levels ($P < 0.001$) but not with chloride concentrations. Opportunities exist for follow-up studies of perchlorate's origins using isotope forensics and for further elucidation of the role of atmospheric processes in the formation or transport of perchlorate.","ISSN":"0013-936X","note":"PMID: 18441789","shortTitle":"Perchlorate in groundwater","journalAbbreviation":"Environ. Sci. Technol.","language":"eng","author":[{"family":"Parker","given":"David R."},{"family":"Seyfferth","given":"Angelia L."},{"family":"Reese","given":"Brandi Kiel"}],"issued":{"date-parts":[["2008",3,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Each of the perchlorate treatment technologies evaluated in this analysis (ion exchange, biological treatment, and reverse osmosis) can also remove co-occurring nitrate [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"cS5tQE6t","properties":{"formattedCitation":"(Water Research Foundation,

2014)","plainCitation":"(Water Research Foundation, 2014)","noteIndex":0},"citationItems":[{"id":172,"uris":["http://zotero.org/groups/945096/items/YB3TVMYJ"],"uri":["http://zotero.org/groups/945096/items/YB3TVMYJ"],"itemData":{"id":172,"type":"article-journal","title":"Perchlorate in Drinking Water: Regulatory Update and Treatment Options","page":"3","source":"Zotero","language":"en","author":[{"literal":"Water Research Foundation"}],"issued":{"date-parts":[["2014"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. For biological treatment and reverse osmosis, nitrate removal would be continuous along with perchlorate throughout operation. Ion exchange run to full exhaustion for perchlorate without consideration of nitrate breakthrough, however, could result in a "peaking" situation. Peaking can occur when nitrate adsorbed early in the resin's life is displaced by competing perchlorate, resulting in a treated water concentration of nitrate greater than the influent concentration. Therefore, perchlorate-selective ion exchange would require careful operation to maintain nitrate removal throughout the process. A quantitative evaluation of the potential benefits associated with the added advantage of nitrate removal was not included in this benefits assessment.

In the *Office of Inspector General: Scientific Analysis of Perchlorate* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rJD7MSTE","properties":{"formattedCitation":"(U.S. EPA, 2008b)","plainCitation":"(U.S. EPA, 2008b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":966,"uris":["http://zotero.org/groups/945096/items/IQ4YKBMA"],"uri":["http://zotero.org/groups/945096/items/IQ4YKBMA"],"itemData":{"id":966,"type":"article-journal","title":"OIG Scientific Analysis of Perchlorate External Review Draft","page":"213","source":"Zotero","language":"en","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the EPA suggested that the best approach to conduct a risk assessment for perchlorate would include all four NIS stressors acting on the thyroid: thiocyanate, nitrate, perchlorate, and lack of iodide. Perchlorate is a strong NIS inhibitor; however, exposure to humans may be relatively low. In contrast, nitrate and thiocyanate are weak NIS inhibitors; however, exposure levels to these two chemicals are much greater than perchlorate [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"i8CWv09R","properties":{"formattedCitation":"(U.S. EPA, 2008b)","plainCitation":"(U.S. EPA, 2008b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":966,"uris":["http://zotero.org/groups/945096/items/IQ4YKBMA"],"uri":["http://zotero.org/groups/945096/items/IQ4YKBMA"],"itemData":{"id":966,"type":"article-journal","title":"OIG Scientific Analysis of Perchlorate External Review Draft","page":"213","source":"Zotero","language":"en","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2008"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Consequently, reductions of the co-occurring contaminant nitrate could lead to additional health benefits.

4.3.4 Improved Public Perception of Water Quality

PWS customers may avoid using tap water when they believe it is contaminated and poses health risks. When the public perception of water quality declines, consumers purchase bottled water or point-of-use (POU) filters if they have the means to do so.

In addition or as an alternative, they may avoid the use of tap water, ingesting and cooking with other liquids, substituting pre-mixed baby formula, and using other strategies to limit ingestion. Consumer avoidance of tap water sources usually results in costs to the consumers, either in the cost of obtaining substitute fluids or in potential health impacts of reduced fluid intake.

The relationship between perchlorate in tap water and changes in consumer behavior is a complex one. Factors that impact the choice to avoid tap water depend on public information that is provided on levels of the contamination, potential health effects, individual aversions to risk taking, and other considerations. A quantitative evaluation of these responses and the potential benefits of avoiding associated costs to the consumer or governments is not included in this benefits assessment. Nevertheless, consumers purchase bottled water or invest in other methods of improving drinking water quality, such as POU devices, specifically to avoid ingestion of contaminants such as perchlorate. Thus, it is possible that a reduction in perchlorate contamination may reduce mitigation expenditures.

5 Economic Impact and Cost Analysis

This chapter presents estimates of the total national costs of the proposed perchlorate rule. To estimate the national costs of the rule, the EPA calculated the incremental costs of rule components associated with the proposed rule compared to the current requirements under the SDWA. Specifically, the costs associated with the proposed rule include (1) costs borne by water systems to comply with the new NPDWR, and (2) costs to the primacy agencies to implement and enforce the NPDWR.

Costs to water systems include monitoring costs, treatment costs, and administrative costs. For treatment costs, the EPA identified the treatment technologies that will be used to comply with the MCL and estimates capital costs and operating and maintenance (O&M) costs for these technologies [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZWJdzdEq","properties":{"formattedCitation":"(USEPA, 2018g)","plainCitation":"(USEPA, 2018g)","noteIndex":0},"citationItems":[{"id":977,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":977,"type":"report","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Administrative costs to water systems include one-time costs to understand the rule and provide training, as well as ongoing costs for activities associated with compliance monitoring (i.e., sampling, applying for waivers, and reporting of compliance results).

Similarly, primacy agencies (states, territories, and tribal nations) incur one-time administrative costs for reading and understanding the rule, and modifying existing regulations. Ongoing administrative costs to primacy agencies include labor costs for reviewing compliance monitoring reports, making determinations on monitoring waivers, and reviewing proposed changes in treatment.

For the analysis of costs, the EPA used the PWS and occurrence data described in Sections [REF _Ref523415085 \r \h] and [REF _Ref523404705 \r \h], with exceptions as noted.

Section [REF _Ref523415174 \r \h] summarizes methods used to identify systems that may need to control perchlorate to meet the MCL and estimate associated control costs. Section [REF _Ref523415193 \r \h] describes the methods used to estimate the monitoring and administration costs for PWSs and primacy agencies. Section [REF _Ref535302370 \r \h] presents the total cost results, and Section [REF _Ref535302385 \r \h] summarizes household-level costs for affected systems with control costs.

5.1 Control Costs Method

The EPA assumed that the entry points with exceedances will need to implement a control technology to comply with the proposed MCL or alternative MCL. The cost method overview in this section includes brief technology descriptions (Section [REF _Ref523455076 \r \h *

MERGEFORMAT]), a brief discussion of the Agency's treatment cost estimating tools, and assumptions about compliance options (Section [REF _Ref535311709 \r \h]).

5.1.1 Description of Available Control Technologies

The EPA has identified the following technologies as effective for the removal of perchlorate from drinking water:

- Ion exchange;
- Biological treatment;
- Centralized reverse osmosis; and
- POU reverse osmosis.

In addition, there are non-treatment options such and changing source water that might be used in lieu of treatment to comply with a perchlorate standard. The sections below describe each of the technologies and non-treatment options, along with key assumptions and scenarios used to estimate unit costs for each. The document *Technologies and Costs for Treating Perchlorate-Contaminated Waters* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"wyr7sZ4c","properties":{"formattedCitation":"(USEPA, 2018g)","plainCitation":"(USEPA, 2018g)","noteIndex":0},"citationItems":[{"id":977,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":977,"type":"report","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] contains a more complete discussion of the technologies and cost estimating method.

5.1.1.1 Ion Exchange

Ion exchange is a physical/chemical separation process in which an ion (such as perchlorate) in the feed water is exchanged for an ion (typically chloride) on a resin generally made of synthetic beads or gel. A variety of resin types have been tested for perchlorate removal. These resin types include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base polyacrylic, weak-base polystyrenic, and perchlorate-selective.[11]

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[11] While Tripp et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"SGLaAt6R","properties":{"formattedCitation":"(2003)","plainCitation":"(2003)","noteIndex":11},"citationItems":[{"id":988,"uris":["http://zotero.org/groups/945096/items/J24BWNQH"],"uri":["http://zotero.org/groups/945096/items/J24BWNQH"],"itemData":{"id":988,"type":"article","title":"Treatment of perchlorate in groundwater by ion exchange technology","publisher":"AWWA Research Foundation","call-number":"Publication No. 909","author":[{"family":"Tripp","given":"A.R."},{"family":"Clifford","given":"D."},{"family":"Roberts","given":"D.J."},{"family":"Cang","given":"Y."},{"family":"Aldridge","given":"L."},{"family":"Gillogly","given":"T."},{"family":"Boulos","given":"L."}],"issued":{"date-parts":[["2003"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] also examined strong base polyvinylpyridine resins, comparable quantitative data on their removal efficiency are not available.

In application, feed water passes through a bed of resin in a vessel or column. The operation typically continues until the resin is exhausted, meaning that the chloride on enough of the resin's available exchange sites has been replaced with ions from the feed water so that the resin is no longer effective for removing the ion. At this point, the resin may be disposed of and replaced or regenerated. The length of time until resin exhaustion and replacement or regeneration is a critical factor in the cost-effectiveness of ion exchange as a treatment technology. It is typically measured by the number of bed volumes of water that can be treated before the breakthrough of perchlorate and can vary based on a variety of factors, including the type of resin used.

Based on data from full-scale operations, it is likely that most systems using ion exchange to comply with a perchlorate MCL would use a perchlorate-selective resin that would be disposed of, rather than regenerated, when exhausted. The ion exchange unit costs presented here assume the use of perchlorate-selective resin in two scenarios. The first scenario assumes the resin bed treats 250,000 bed volumes before disposal and replacement. The second scenario assumes 170,000 bed volumes. Both scenarios assume disposal of the spent resin by incineration, although some systems might have the slightly cheaper option of landfill disposal available. Perchlorate-selective resins are unlikely to remove substantial amounts of co-occurring contaminants because the resins maximize perchlorate removal at the expense of removing co-occurring contaminants like nitrate. Therefore, ancillary benefits are unlikely to occur.

5.1.1.2 Biological Treatment

Biological treatment of perchlorate uses bacteria to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. Biological treatment offers complete destruction of the perchlorate ion, eliminating the need for management of perchlorate-bearing waste streams. Although biological treatment is a relatively new technology for the treatment of drinking water in the United States, the State of California has identified biological treatment (along with ion exchange) as one of two best available technologies for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). The first full-scale facility using biological treatment of perchlorate to supply municipal drinking water began operation in 2016 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"sMXmpIso","properties":{"formattedCitation":"(Webster and Crowley, 2016; Webster and Litchfield, 2017)","plainCitation":"(Webster and Crowley, 2016; Webster and Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":989,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":989,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":990,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":990,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-

parts":[["2017"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The most promising designs for biological treatment of perchlorate at drinking water facilities are those that operate either in a fixed bed or a fluidized bed configuration. Both fixed bed and fluidized bed designs involve a media bed that provides a surface on which perchlorate-reducing bacteria grow. For fixed bed reactors, influent water is typically passed under pressure through a static media bed located in a vessel. An alternative fixed bed design uses a gravity-fed concrete basin to hold the biologically active media. Fluidized bed bioreactor designs use vessels where high influent rates in an up-flow design fluidize the media bed, allowing for more surface area for biomass growth. The biological treatment unit costs presented here consider three design scenarios: a fixed bed using pressure vessels, a fixed bed using gravity basins, and a fluidized bed.

5.1.1.3 Centralized Reverse Osmosis

Membrane filtration processes physically remove perchlorate ions from drinking water. These processes separate a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at a pressure greater than the normal osmotic pressure. The membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane and are removed as concentrate, or reject. This technique does not destroy the perchlorate ion and, therefore, creates a subsequent need for disposal or treatment of the perchlorate-contaminated waste (the concentrate).

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by the electrostatic repulsion of ions from the charged membrane surface. Membrane filtration technologies evaluated for perchlorate treatment include reverse osmosis, nanofiltration, and ultrafiltration. Bench studies of nanofiltration and ultrafiltration membranes show significant variability in these membranes' abilities to remove perchlorate, depending on other constituents of the source water. Across multiple studies, however, reverse osmosis membranes consistently achieve perchlorate removal by up to 95–98 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"dFA9xEYZ","properties":{"formattedCitation":"(Liang et al., 1998; Nam et al., 2005; Sanyal et al., 2015; Yoon, Amy, et al., 2005; Yoon, Yoon, et al., 2005)","plainCitation":"(Liang et al., 1998; Nam et al., 2005; Sanyal et al., 2015; Yoon, Amy, et al., 2005; Yoon, Yoon, et al., 2005)","noteIndex":0},"citationItems":[{"id":985,"uris":["http://zotero.org/groups/945096/items/IQVVPD73"],"uri":["http://zotero.org/groups/945096/items/IQVVPD73"],"itemData":{"id":985,"type":"paper-conference","title":"Investigation of Treatment Options for Perchlorate Removal.","publisher":"La Verne, CA: Metropolitan Water District of Southern California","publisher-place":"San Diego, CA","event":"AWWA Water Quality Technology Conference","event-place":"San Diego, CA","author":[{"family":"Liang","given":"S."},{"family":"Scott","given":"K.N."},{"family":"Palencia","given":"L.S."},{"family":"Bruno","given":"J."}],"issued":{"date-parts":[["1998"]]}}},{"id":986,"uris":["http://zotero.org/groups/945096/items/YHEV76YW"],"uri":["http://zotero.org/groups/945096/items/YHEV76YW"],"itemData":{"id":986,"type":"paper-conference","title":"Perchlorate Rejection by High-Pressure Membranes and Brine Stream Treatment by Chemical and Biological Processes.","publisher-place":"Phoenix,

AZ","event":"American Water Works Association Membrane Technology Conference","event-place":"Phoenix,
AZ","author":[{"family":"Nam","given":"S."},{"family":"Kim","given":"S."},{"family":"Choi","given":"H."},{"family":"Yoon","given":""},{"family":"Silverstein","given":"J."},{"family":"Amy","given":"G."}],"issued":{"date-parts":[["2005"]]}}},{"id":987,"uris":["http://zotero.org/groups/945096/items/VTUDRPDL"],"uri":["http://zotero.org/groups/945096/items/VTUDRPDL"],"itemData":{"id":987,"type":"article-journal","title":"Design of ultrathin nanostructured polyelectrolyte-based membranes with higher perchlorate rejection and high permeability","container-title":"Separation and Purification Technology","volume":"145","issue":"113-119","author":[{"family":"Sanyal","given":"O."},{"family":"Sommerfeld","given":"A.N."},{"family":"Lee","given":"I."}],"issued":{"date-parts":[["2015"]]}}},{"id":992,"uris":["http://zotero.org/groups/945096/items/HPHVBSWB"],"uri":["http://zotero.org/groups/945096/items/HPHVBSWB"],"itemData":{"id":992,"type":"article-journal","title":"Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes.","container-title":"Water Science and Technology","page":"327-334","volume":"51","issue":"6-7","author":[{"family":"Yoon","given":"J."},{"family":"Amy","given":"G."},{"family":"Yoon","given":"Y."}],"issued":{"date-parts":[["2005"]]}}},{"id":991,"uris":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"uri":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"itemData":{"id":991,"type":"article-journal","title":"Determination of perchlorate rejection and associated inorganic fouling (scaling) for reverse osmosis and nanofiltration membranes under various operating conditions","container-title":"Journal of Environmental Engineering","page":"726-733","author":[{"family":"Yoon","given":"J."},{"family":"Yoon","given":"Y."},{"family":"Amy","given":"G."},{"family":"Her","given":"N."}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The centralized reverse osmosis unit costs presented here assume the use of relatively low-pressure reverse osmosis membrane elements (consistent with the type of elements shown to be effective in the literature) to remove perchlorate. The designs on which the unit costs are based achieve recovery rates from 70 percent to 85 percent, meaning 15 to 30 percent of the influent water becomes perchlorate-laden concentrate. The unit costs assume discharge of this concentrate to a publicly owned treatment works (POTW). Although it might be impractical for most POTWs to treat very large concentrate flows, this assumption results in more conservative estimates (i.e., erring on the side of higher costs) than surface water (ocean) discharge or deep well injection, options that might be available to a limited number of systems.

5.1.1.4 POU Reverse Osmosis

For perchlorate removal, the National Science Foundation (NSF) Joint Committee on Drinking Water Treatment Units has added a protocol to the *NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems* that requires a reverse osmosis unit to be able to reduce perchlorate from a challenge level of 130 µg/L to a target level of 4 µg/L [ADDIN ZOTERO_ITEM CSL_CITATION
{"citationID":"0rSQe3eF","properties":{"formattedCitation":"(NSF International,

2004)","plainCitation":"(NSF International,
2004)","noteIndex":0},"citationItems":[{"id":997,"uris":["http://zotero.org/groups/945096/items/
9EAEK7S4"],"uri":["http://zotero.org/groups/945096/items/9EAEK7S4"],"itemData":{"id":997,
"type":"webpage","title":"Perchlorate
Reduction","URL":"http://www.nsf.org/consumer/drinking_water/perchlorate_reduction.asp","a
uthor":[{"literal":"NSF International"}],"issued":{"date-
parts":[["2004"]]}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}]. NSF International, the Underwriters Laboratories, and the Water Quality Association provide third-party testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media.

The operating principle for POU reverse osmosis devices is the same as centralized reverse osmosis: steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to a reverse osmosis membrane for dissolved ion removal, POU reverse osmosis devices often have a sediment pre-filter and a carbon filter in front of the reverse osmosis membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

The POU reverse osmosis unit costs the EPA developed [ADDIN ZOTERO_ITEM
CSL_CITATION {"citationID":"mVTmCCMo","properties":{"formattedCitation":"(USEPA,
2018g)","plainCitation":"(USEPA,
2018g)","noteIndex":0},"citationItems":[{"id":977,"uris":["http://zotero.org/groups/945096/item
s/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":9
77,"type":"report","title":"Technologies and Costs for Treating Perchlorate-Contaminated
Waters","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-
parts":[["2018"]]}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}] assume small drinking water systems would purchase, install, and maintain certified POU devices for all customers. When a system installs, controls (i.e., owns), and maintains POU devices at all customer locations where water is consumed (e.g., residences), it can forego centralized treatment [ADDIN ZOTERO_ITEM
CSL_CITATION {"citationID":"hwkrqREN","properties":{"formattedCitation":"(USEPA,
2006a)","plainCitation":"(USEPA,
2006a)","noteIndex":0},"citationItems":[{"id":987,"uris":["http://zotero.org/groups/945096/item
s/SAEYMT7G"],"uri":["http://zotero.org/groups/945096/items/SAEYMT7G"],"itemData":{"id":
987,"type":"report","title":"Point-of-Use or Point-of-Entry Treatment Options for Small
Drinking Water Systems","collection-title":"EPA-815-R-06-010","publisher":"USEPA, Office of
Ground Water and Drinking Water, Standards and Risk Management Division","publisher-
place":"Washington, D.C.","event-place":"Washington,
D.C.","author":[{"family":"USEPA","given":""}],"issued":{"date-
parts":[["2006"]]}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}]. The costs also include development of a public education program and monitoring of the POU devices.

5.1.1.5 Non-Treatment Alternatives

For small water utilities that lack the financial and/or technical capacity to implement a new treatment-based compliance strategy, non-treatment options may offer a more cost-effective path

to compliance. Non-treatment options essentially replace the contaminated water source with water that meets drinking water standards, including a new standard for perchlorate.

Non-treatment solutions for drinking water compliance include well rehabilitation, contaminant source elimination, new well construction, and interconnecting with another system to purchase water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"lK26Qjmg","properties":{"formattedCitation":"(USEPA, 2006b)","plainCitation":"(USEPA, 2006b)","noteIndex":0},"citationItems":[{"id":986,"uris":["http://zotero.org/groups/945096/items/3SWI97AY"],"uri":["http://zotero.org/groups/945096/items/3SWI97AY"],"itemData":{"id":986,"type":"article","title":"Technology and Cost Document for the Final Ground Water Rule","publisher":"EPA-815-R-06-015","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2006"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The feasible non-treatment options will depend on site-specific circumstances such as system size, source water type, contaminant reduction needs, and proximity to alternative water sources. For small systems, neither the well rehabilitation for contaminated groundwater sources nor source elimination (e.g., remediation of perchlorate-contaminated sediments or groundwater) is likely to be a feasible and cost-effective solution. Another option – blending water from existing wells – may be a feasible, low-cost option for systems with multiple wells, including some for which perchlorate does not exceed the proposed perchlorate standard. For systems that cannot blend source water to comply with the proposed standard, two feasible non-treatment options include a new well to replace the contaminated source water and an interconnection to purchase water from a supplier. These two options are likely to have higher costs than the other options [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"nVsZ7M6v","properties":{"formattedCitation":"(USEPA, 2006b)","plainCitation":"(USEPA, 2006b)","noteIndex":0},"citationItems":[{"id":986,"uris":["http://zotero.org/groups/945096/items/3SWI97AY"],"uri":["http://zotero.org/groups/945096/items/3SWI97AY"],"itemData":{"id":986,"type":"article","title":"Technology and Cost Document for the Final Ground Water Rule","publisher":"EPA-815-R-06-015","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2006"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

The non-treatment unit costs presented here consider two scenarios: interconnecting with another system and drilling a new well to replace a contaminated one. The costs associated with drilling a new well include well casing, screens, plugs, and pumps; well installation; buried piping and valves to connect the new well to the system; and operator labor, materials, and energy for operating and maintaining the well pumps and valves. The interconnection option involves laying a pipeline to connect the affected system to the distribution network of a neighboring system that can provide adequate water that meets all applicable drinking water standards. Costs include construction of a buried interconnecting pipeline and valves, the cost of purchased water, and maintenance of the pipeline.

5.1.2 Treatment Assumptions and Unit Costs

To generate unit costs for the treatment technologies and non-treatment alternatives discussed above, the EPA used its work breakdown structure (WBS) cost-estimating models. The WBS models are spreadsheet-based engineering models for individual treatment technologies that are

linked to a central database of component unit costs. Each WBS model contains the work breakdown for a particular treatment process, and preprogrammed engineering criteria and equations that estimate equipment requirements for user-specified design requirements (e.g., system size and influent water quality). Based on these user-specific inputs, each model generates outputs that include total capital cost and annual O&M cost.

The EPA used the WBS models to generate total capital and O&M cost estimates for each technology and non-treatment option for up to 49 different system flow rates. The EPA generated separate estimates that correspond to different water sources (groundwater or surface water), three different cost levels (low, mid, and high), and different technology-specific scenarios (e.g., 250,000 or 170,000 bed volumes for ion exchange). The EPA then fit cost equations to the resulting WBS estimates for each scenario modeled, and separately for total capital and for O&M costs. The cost equations for total capital costs depend on system peak production or design flow, measured in million gallons per day (MGD). The equations for O&M cost depend on average daily flow in MGD. For each scenario, the EPA fit up to three curves: one covering small systems (less than 1 MGD design flow), one covering medium systems (1 MGD to less than 10 MGD design flow), and one covering large systems (10 MGD design flow and greater). The document *Technologies and Costs for Treating Perchlorate-Contaminated Waters* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aKrrsfCv","properties":{"formattedCitation":"(USEPA, 2018g)","plainCitation":"(USEPA, 2018g)","noteIndex":0},"citationItems":[{"id":977,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":977,"type":"report","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] contains a more complete discussion of the WBS models and the cost-estimating approach.

For each entry point in the UCMR 1 dataset, the EPA compared the maximum perchlorate concentration to the MCL, and identified those that have a concentration that exceeds the MCL. These entry points may incur some control costs to comply with the proposed rule. The EPA estimated design and average flows based on entry point populations using the method described in section [REF _Ref536806570 \r \h] and a blending ratio. Based on the flows, the EPA used the cost curves to compare costs across the technologies, which indicated that ion exchange with perchlorate-selective resin was the most cost-effective option. This outcome is consistent with the treatability literature, which contains substantially more full-scale ion exchange treatment plants compared to biological treatment or reverse osmosis. Therefore, the EPA used the capital cost and O&M cost curves to estimate treatment costs using the following assumptions:

- perchlorate selective resin with 170,000 bed volumes;
- 95 percent removal effectiveness;
- 80 percent safety factor (e.g., treatment target 14.4 µg/L for an MCL of 18 µg/L); and
- Design and average flow rates reflect the use of blending of treated and non-treated water to meet the treatment target.

[REF _Ref535312062 \n \h] provides the cost curves used in this analysis. It also contains the formula used to calculate a blending ratio.

5.2 Administrative and Monitoring Costs Method

Although added treatment improves drinking water quality and, therefore, health risk reductions and benefits, there are additional costs of the proposed rule. There are several implementation activities that must occur before systems adopt treatment to comply with an MCL. These activities result in the following costs:

- **State administrative costs.** States incur costs associated with adopting and enforcing the NPDWR and administering compliance monitoring programs. Each state must conduct one-time activities: reading and understanding the rule, and modifying existing state regulations. Other state costs are per entry point, and include reviewing compliance monitoring reports and making determinations on monitoring waivers.
- **Sampling costs.** PWSs incur O&M and labor costs for taking and analyzing a single water sample. The EPA assumes that all PWS size categories are subject to the same per-sample costs. Since these costs are per entry point, the cost per PWS may reflect multiple entry points.
- **Other PWS administrative costs.** Administrative costs may be per PWS or per entry point. Activities that result in administrative costs per PWS include reading the rule and providing training. Administrative costs per entry point include those for applying to the state for a monitoring waiver and reporting of compliance monitoring results.

As noted in Section [REF _Ref523347586 \r \h], California and Massachusetts are excluded from the analysis of treatment-related costs and benefits. However, the EPA expects that California and Massachusetts will incur one-time administrative costs to read and understand the rule. As such, these states are included in the counts and costs for one-time primacy agency costs, but system counts, monitoring, waiver, and control costs exclude these states.

5.2.1 Labor Rates

Because the administrative and monitoring activities primarily require labor time, the EPA estimated current labor rates for the cost analysis. State labor rates are based on the mean hourly wage rate from the BLS Standard Occupational Classification code 19-2041 (State Government – Environmental Scientists and Specialists, Including Health). Wages are loaded using a factor calculated from the BLS Employer Costs for Employee Compensation report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"AyQYarRv","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","plainCitation":"(Bureau of Labor Statistics (BLS), 2016 Table 3)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"uri":["http://zotero.org/groups/945096/items/L8X3BDZ9"],"itemData":{"id":984,"type":"webpage","title":"Employer Cost for Employee Compensation -- September 2016","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2016"]]},"label":"book","suffix":"Table 3"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], for a fully loaded hourly wage rate of $50.67 for states.

To estimate costs to PWSs associated with compliance monitoring and other administrative costs, the EPA used the labor rates in the WBS models for technical staff (i.e., treatment plant operators) and managerial staff (i.e., utility managers for smaller systems and environmental managers for larger systems). The labor rates are in 2017 dollars and include wages and benefits. They vary by occupation and by water system size: technical rates range from $31.91 per hour for systems up to 3,300 people to $43.84 per hour for systems serving more than 100,000 people; and managerial rates range from $45.24 to $71.85 across system size categories. The EPA estimated a weighted average wage rate of $34.71. This average rate incorporates within-size category weights for a mix of managerial and technical labor time based on employment data in the *2006 Community Water System Survey* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"vMhubruh","properties":{"formattedCitation":"(USEPA, 2009c)","plainCitation":"(USEPA, 2009c)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and across-size category weights based on the number of systems. [REF _Ref535312062 \n \h] provides data and calculation details.

5.2.2 Labor Hours

As described above, PWSs and states will both include monitoring and administrative costs, including one-time costs, and recurring monitoring and waiver application costs. [REF _Ref523410484 \h] shows the activities, frequency, and hours per activity for primacy agencies (including 49 states, 1 tribal nation, and 5 territories). [REF _Ref536806569 \h] itemizes the administrative and monitoring activities for PWSs, and shows the frequency and number of hours for each activity.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Labor Hours for Primacy Agency Administrative Requirements

Activity	Frequency	Hours
Read and understand the rule, adopt regulatory changes[a]	One time per state	416
Provide training and assistance to PWSs	One time per state	2,080
Provide training to staff and systems	One time per state	250
Review waiver applications	Once every 9 years per eligible system	8
Review monitoring reports	Per monitoring event[b]	1

a. The EPA assumed that two states that already regulate perchlorate in drinking water would not incur most of the burdens listed, but included 40 hours for this activity.
b. See Section [REF _Ref532278116 \r \h] for monitoring frequency requirements.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Labor Hours for Drinking Water Systems' Administrative and Monitoring Requirements

Activity	Frequency	Hours	
		Small Systems	Large Systems
Read the rule	One time per system	4	4
Provide training	One time per system	16	32
Apply to state for monitoring waiver	Once every 9 years per eligible system	16	16
Take and analyze a single finished water sample	Per monitoring event[a]	1	1

a. See Section [REF _Ref532278116 \r \h] for monitoring frequency requirements.

5.2.3 Analytical Costs for Monitoring

PWSs will also incur analytical costs for each water sample. The EPA assumes that these costs will be in the range of $64 per sample based on an average of costs per sample from laboratories [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Ftv0lunK","properties":{"formattedCitation":"(Eurofins, 2016; TestAmerica Laboratories, 2015; Utah Department of Environmental Quality (Utah DEQ), 2016)","plainCitation":"(Eurofins, 2016; TestAmerica Laboratories, 2015; Utah Department of Environmental Quality (Utah DEQ), 2016)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1003,"uris":["http://zotero.org/groups/945096/items/EZMGVZEJ"],"uri":["http://zotero.org/groups/945096/items/EZMGVZEJ"],"itemData":{"id":1003,"type":"article","title":"Seafood Products Association (SPA) -- Eurofins Pricing Document","author":[{"family":"Eurofins","given":""}],"issued":{"date-parts":[["2016"]]}}},{"id":1005,"uris":["http://zotero.org/groups/945096/items/S8P2VE4W"],"uri":["http://zotero.org/groups/945096/items/S8P2VE4W"],"itemData":{"id":1005,"type":"article","title":"General Services Administration Federal Acquisition Services (FAS) Authorized Federal List Price","author":[{"family":"TestAmerica Laboratories","given":""}],"issued":{"date-parts":[["2015"]]}}},{"id":1004,"uris":["http://zotero.org/groups/945096/items/WXXSZDNZ"],"uri":["http://zotero.org/groups/945096/items/WXXSZDNZ"],"itemData":{"id":1004,"type":"article","title":"Laboratory Costs and Sampling Procedures","author":[{"literal":"Utah Department of Environmental Quality (Utah DEQ)"}],"issued":{"date-parts":[["2016"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

5.2.4 Costs per Administrative/Monitoring Event

Based on the hours per activity, the labor rates for PWSs and primacy agencies, and the analytical costs for monitoring, the EPA calculated a per-activity cost for PWSs and primacy agencies, as shown in [REF _Ref523411577 \h]. As noted above, California and Massachusetts are assumed to incur upfront costs to read and understand the rule, but will not incur incremental costs to provide training, or to review waiver applications or monitoring reports.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Costs per Administrative/Monitoring Event for PWSs and Primacy Agencies

Event	PWS		Primacy Agencies	
	Small	Large	Included	Excluded
Monitoring	$99	$99	$51	$0
Waiver application	$555	$555	$405	$0
Read the rule, provide training, adopt regulatory or programmatic changes	$694	$1,249	$139,140	$2,027

5.2.5 Number of Monitoring Events

The EPA estimated costs for two phases of perchlorate monitoring: the initial monitoring and long-term monitoring. The Agency assumed that initial perchlorate monitoring requirements will be phased in over a period of six years following the effective date. Monitoring requirements vary by size and type of system. Large CWSs will collect initial monitoring samples during the first three years following the effective date (i.e., years four to six of the analysis period); the EPA assumed that one-third of these systems would collect samples per year. Small CWSs and NTNCWSs would collect initial monitoring samples in the subsequent three-year period (i.e., years seven to nine of the analysis period). The EPA assumed that, within these periods, all systems would conduct initial monitoring – one year of quarterly monitoring to determine whether perchlorate concentrations are consistently and reliably below the proposed MCL.

The schedule for long-term monitoring is based on the EPA's Standardized Monitoring Framework for drinking water contaminants [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"HlJYZ8nR","properties":{"formattedCitation":"(USEPA, 1991; 2004)","plainCitation":"(USEPA, 1991; 2004)","noteIndex":0},"citationItems":[{"id":169,"uris":["http://zotero.org/groups/945096/items/ZSHKRHSY"],"uri":["http://zotero.org/groups/945096/items/ZSHKRHSY"],"itemData":{"id":169,"type":"article","title":"Standardized Monitoring Framework","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["1991",2]]}}},{"id":993,"uris":["http://zotero.org/groups/945096/items/XIN79HTB"],"uri":["http://zotero.org/groups/945096/items/XIN79HTB"],"itemData":{"id":993,"type":"article","title":"The Standardized Monitoring Framework: A Quick Reference Guide","publisher":"EPA-816-F-04-010","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2004"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Under this framework, systems with MCL exceedances would continue to monitor quarterly, while systems below the MCL that obtain waivers will monitor annually for three years (surface water systems) or triennially for nine years (groundwater systems), and then incur costs for a waiver application. Thereafter, these systems will continue reduced monitoring – once every nine years – under subsequent waivers. Systems that are below the MCL without waivers will monitor once yearly (surface water systems) or once every three years (groundwater).

For other inorganic contaminants with MCLs currently in place (e.g., mercury), the EPA assumes that 90 percent of eligible systems with groundwater sources apply for and receive system-specific waivers; for eligible systems with surface water sources, this proportion is

40 percent [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"nRvPG48F","properties":{"formattedCitation":"(USEPA, 2008c)","plainCitation":"(USEPA, 2008c)","noteIndex":0},"citationItems":[{"id":989,"uris":["http://zotero.org/groups/945096/items/QSXYHBID"],"uri":["http://zotero.org/groups/945096/items/QSXYHBID"],"itemData":{"id":989,"type":"article","title":"Draft Information Collection Request for the Disinfectants/Disinfection Byproducts, Chemical, and Radionuclides Rule","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2008",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The EPA also applied this assumption in this analysis.

[REF _Ref530148157 \h * MERGEFORMAT] summarizes the timing of expected activities for affected entities based on the requirements.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Schedule of Administrative Requirements

Year	Primacy Agencies	Large CWS	NTNCWS and Small CWS
1	Read/understand rule, adopt rule, and training		
2			
3			
4	Review monitoring reports and waiver applications	Conduct initial monitoring; implement treatment	
5			
6			
7		Monitor per Standardized Monitoring Framework	Conduct initial monitoring; implement treatment
8			
9			
10			Monitor per Standardized Monitoring Framework
11			
12			
13			
14			
15			
16			
17			
18			
19			
20 and after			

The monitoring schedule based on the Standardized Monitoring Framework is per entry point. To estimate the number of monitoring events per PWS, the EPA estimated the average number of entry points for very small, small, medium, large, and very large PWSs (with categories based on the population served) based on the occurrence data [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NoXLDRl7","properties":{"formattedCitation":"(USEPA, 2018d)","plainCitation":"(USEPA,

2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], as described in Section [REF _Ref524938747 \r \h]. [REF _Ref524939687 \h] summarizes the average number of entry points per PWS based on population served. For PWSs that were included in the occurrence data, EPA used the number of entry points from that dataset. For PWSs not included in the occurrence data, EPA used the average number of entry points based on the population served from [REF _Ref524939687 \h].

5.3 Total Cost Results

The EPA estimated the costs over a 35-year analysis period and assumed that control technologies would be implemented by the end of the initial monitoring phase (e.g., by year six for large CWSs; if small CWSs or NTNCWSs incurred control costs, those costs would be phased in by year nine). The EPA calculated the present value of total costs in each year of the analysis period and discounted to rule finalization using both a 3 percent and 7 percent discount rate. [REF _Ref523412826 \h] and [REF _Ref525891735 \h] summarize the results at MCLs of 56 µg/L and 18 µg/L, respectively.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Summary of Total Annualized Costs at an MCL of 56 µg/L (millions 2017$)

Cost Component	3% Discount	7% Discount
Drinking water systems costs		
Treatment costs[a]	$0.65	$0.70
Monitoring and administration[b]	$5.93	$6.38
Drinking water systems total	$6.58	$7.07
State costs		
Administration	$3.09	$3.20
Total costs	***$9.67***	***$10.28***

a. The values shown are the mid-cost estimates. Low-cost estimates are 1% to 2% lower than the mid-cost estimates at the 3% and 7% discount rates, respectively; the high-cost estimates are 13% to 20% higher across discount rates.
b. Costs include monitoring for all CWSs and NTNCWSs. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate, provided the states allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on the system and state decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.
Note: Totals may not sum because of rounding.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Summary of Total Annualized Costs at an MCL of 18 µg/L (millions 2017$)

Cost Component	UCMR 1		National[a]	
	3% Discount	7% Discount	3% Discount	7% Discount
Drinking water systems costs				
Treatment costs[b]	$6.92	$7.29	$7.92	$8.37
Monitoring and administration[c]	$5.94	$6.38	$5.94	$6.38
Drinking water systems total	$12.85	$13.67	$13.86	$14.75
State costs				
Administration	$3.09	$3.21	$3.09	$3.21
Total costs	***$15.95***	***$16.88***	***$16.95***	***$17.96***

a. The EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is 1 of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the six UCMR 1 systems in the stratum. Overall, the stratum population served accounts for 1.32% of the national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers may be exposed to perchlorate greater than 18 µg/L. Based on this population estimate, the EPA calculated per-capita costs for the system and extrapolated them to national levels.
b. The values shown are the mid-cost estimates. Low-cost estimates are 1% to 2% lower than the mid-cost estimates at the 3% and 7% discount rates, respectively; the high-cost estimates are 13% to 20% higher across discount rates.
c. Costs include monitoring for all CWSs and NTNCWSs. Some consecutive systems that purchase 100% of their water from wholesale systems may not be required to monitor for perchlorate, provided the states allow integrated system agreements to include perchlorate among the monitoring requirements that the wholesale system fulfills for the consecutive system. The potential number of consecutive systems excluded from perchlorate monitoring depends on the system and state decisions and, therefore, is unknown. Excluding monitoring costs for approximately 8,400 consecutive systems that do not report a water source facility (e.g., well or intake) in SDWIS/FED from the monitoring cost analysis reduces annualized monitoring costs by $0.8 million.
Note: Totals may not sum because of rounding.

5.4 Household Costs

Water systems typically recover control costs through increased household rates, resulting in increased costs at the household level. To calculate the magnitude of this cost increase, the EPA first estimated the number of households that may incur costs as a result of the rule based on the population served by affected PWSs and the state-specific average household size [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"fs2jK6J2","properties":{"formattedCitation":"(U.S. Census Bureau, 2017c)","plainCitation":"(U.S. Census Bureau, 2017c)","noteIndex":0},"citationItems":[{"id":985,"uris":["http://zotero.org/groups/945096/items/CGU3LT9N"],"uri":["http://zotero.org/groups/945096/items/CGU3LT9N"],"itemData":{"id":985,"type":"article","title":"Average Household Size of Occupied Housing Units by Tenure. American Community Survey 1-Year Estimates: Table B25010","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. For PWSs that are expected to incur control costs, EPA estimates that approximately 23,893 households will bear increase water rates under an MCL of 56 µg/L. Under an MCL of 18 µg/L, 264,361 households would incur control costs.

The EPA divided the total annual PWS-level costs by the number of households served by the system.

[REF _Ref525046550 \h] summarizes the results. [REF _Ref535312062 \n \h] provides this calculation for each entry point expected to incur control costs. This approach may result in an overestimation of household costs because it assumes that all control costs will be passed to residential customers, although some costs may accrue to industrial or commercial customers.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Summary of Household-Level Annual Control Costs (2017$)

	3% Discount[a]	7% Discount[a]
MCL = 56 µg/L		
Minimum	$11	$14
Average	$40	$47
Maximum	$69	$80
MCL = 18 µg/L[b]		
Minimum	$18	$24
Average	$38	$46
Maximum	$72	$84

a. See [REF _Ref535312080 \n \h] for detailed calculations for all systems.
b. Note that the household-level costs are the same whether or not the small systems costs are extrapolated because the extrapolation is based on per-capita estimated costs.

6 Comparison of Benefits and Costs

6.1 Introduction

This chapter provides a comparison of benefits and costs for each of the regulatory alternatives. The Agency analyzed the costs and benefits of regulating perchlorate concentrations in drinking water to two different MCL standards. In both instances, the MCL is equal to the corresponding MCLG. The alternative MCLG values reflect two approaches to establishing a perchlorate level that is protective of human health.

6.2 Summary of National Costs and Benefits

6.2.1 National Cost Estimates

National compliance costs to PWSs for treatment (both annualized capital and O&M costs); monitoring and administrative activities; and costs to states, including any one-time start-up costs, for regulatory implementation and enforcement, were estimated and described in Chapter 5. [REF _Ref525876134 \h] provides a summary of the national costs for PWSs to comply with the two MCL alternatives for two alternative discount rates.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Summary of Total Annual Costs by Alternative (2017$)

MCL Alternative	UCMR 1		National[a]	
	3% Discount	7% Discount	3% Discount	7% Discount
Preferred MCL (56 µg/L)	$9.67	$10.28	$9.67	$10.28
Alternative MCL (18 µg/L)	$15.95	$16.88	$16.95	$17.96

a. For the proposed MCL of 56 µg/L, the national estimates are the same as the estimates based on UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. For an MCL of 18 µg/L, the EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is 1 of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the 6 UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 775,000 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L. Based on this population estimate, the EPA calculated per-capita costs for the system and extrapolated them to national levels.

6.2.2 National Benefits Estimates

Chapter 4 provided a description of the expected health effects benefits of regulating perchlorate and described a method to quantify avoided IQ decrements in offspring born to pregnant women exposed to perchlorate above alternative MCLs. The Agency estimated national benefits based on discounted lifetime differential earnings estimates for one-point IQ decrements. [REF _Ref525876235 \h] provides a summary of the national benefits for PWSs to comply with the two MCL alternatives for two alternative discount rates.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Summary of Annual Control Benefits by Alternative (Central Estimate; 2017$)

MCL Alternative	UCMR 1		National[a]	
	3% Discount	7% Discount	3% Discount	7% Discount
Preferred MCL (56 µg/L)	$2.12	$0.36	$2.12	$0.36
Alternative MCL (18 µg/L)	$3.87	$0.65	$3.91	$0.66

a. For the proposed MCL of 56 µg/L, the national estimates are the same as the estimates based on UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. For an MCL of 18 µg/L, the EPA applied statistical sampling weights to the results to extrapolate small system results to national results. The entry point at which a measurement exceeds 18 µg/L is 1 of 20 in its sample stratum; no other sample in the stratum had a measurement of perchlorate greater than the minimum reporting level. The entry point population of 2,155 represents 5.31% of the total population served by the 6 UCMR 1 systems in the stratum (40,574). Currently, the stratum population of 775,000 accounts for 1.32% of the 58.7 million national population served by small systems. Thus, the UCMR 1 results indicate that 0.07% (5.31% x 1.32%) of small system customers (approximately 41,100) may be exposed to perchlorate greater than 18 µg/L.

6.3 Comparison of Benefits and Costs

This section provides three comparisons of benefits and costs: a direct comparison of national incremental costs and benefits, a cost-effectiveness analysis, and a break-even analysis. The comparisons include benefits and costs for the proposed MCL of 56 µg/L and the alternative MCL of 18 µg/L.

6.3.1 National Benefit-Cost Comparison

The impact of the proposed rule on national benefits and costs indicates that promulgating an NPDWR for perchlorate is unlikely to result in positive net benefits. [REF _Ref530092144 \h] shows costs, benefits, and net benefits for both MCLs. In both instances, net benefits are negative because costs exceed benefits. The exhibit also shows the incremental costs, benefits, and net benefits between the two MCLs.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Comparison of Incremental Costs and Benefits for Proposed Rule (millions 2017$)

Item	UCMR 1		National[a]	
	3% Discount	7% Discount	3% Discount	7% Discount
MCL = 56 µg/L				
Total annual costs	$9.67	$10.28	$9.67	$10.28
Total annual quantified benefits	$2.12	$0.36	$2.12	$0.36
Total annual quantified net benefits	-$7.55	-$9.92	-$7.55	-$9.92
MCL = 18 µg/L				
Total annual costs	$15.95	$16.88	$16.95	$17.96
Total annual quantified benefits	$3.87	$0.65	$3.91	$0.66
Total annual quantified net benefits	-$12.07	-$16.23	-$13.04	-$17.30
Incremental between 56 and 18 µg/L				
Incremental annual costs	$6.28	$6.60	$7.28	$7.68
Incremental annual quantified benefits	$1.75	$0.29	$1.79	$0.30
Incremental annual quantified net benefits	-$4.53	-$6.31	-$5.49	-$7.38

a. For the proposed MCL of 56 µg/L, the national estimates are the same as the estimates based on the UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 µg/L, national estimates include extrapolation for 1 small system entry point to national estimates based on sampling weights, described above.
Note: There are some slight variations in net benefit differences due to rounding.

6.3.2 Cost-Effectiveness Analysis

Cost-effectiveness analysis provides an alternative way of evaluating costs and benefits. Typically, the analysis involves dividing costs by the quantified benefits such as avoided cases of morbidity. For perchlorate, the EPA considered the cost per avoided IQ decrement. [REF _Ref530093447 \h] shows the cost-effectiveness inputs – total annual costs and annual avoided IQ decrements – and the results for the proposed MCL, the alternative MCL, and the incremental impact between the two MCLs.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Costs per IQ Decrement Avoided (millions 2017$)

Item	UCMR 1		National[a]	
	3% Discount	7% Discount	3% Discount	7% Discount
MCL = 56 µg/L				
Total annual costs	$9.67	$10.28	$9.67	$10.28
Annual avoided IQ decrement (central)	136.12	$136.12	136.12	136.12
Cost per avoided IQ decrement	$0.07	$0.08	$0.07	$0.08
MCL = 18 µg/L				
Total annual costs	$15.95	$16.88	$16.95	$17.96
Annual avoided IQ decrement (central)	248.20	248.20	250.90	250.90
Cost per avoided IQ decrement	$0.06	$0.07	$0.07	$0.07
Incremental between 56 and 18 µg/L				
Total annual costs	$6.28	$6.60	$7.28	$7.68
Annual avoided IQ decrement (central)	112.08	112.08	$114.78	$114.78
Cost change per avoided IQ decrement	-$0.01	-$0.01	$0.00	-$0.01

a. For the proposed MCL of 56 µg/L, the national estimates are the same as the estimates based on the UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 µg/L, national estimates include extrapolation for 1 small system entry point to national estimates based on sampling weights, described above.

6.3.3 Break-Even Analysis

When costs exceed benefits, a break-even analysis identifies what level of quantifiable health risk reduction would be needed to generate benefits that equal costs. For perchlorate, the quantifiable and monetizable health endpoint is avoided IQ decrements. [REF _Ref530094172 \h] shows the inputs to this analysis are the annual costs and unit values for a one-point IQ loss reported in Section [REF _Ref530094326 \r \h]. Dividing the annual cost by the unit value generates an estimate of the avoided IQ decrements that would be needed for benefits to equal costs. For the proposed MCL, these estimates are substantially higher than the estimated rule impact on avoided IQ decrements.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Break-Even Analysis Results (millions 2017$)

Item	UCMR 1		National[a]	
	3% Discount	7% Discount	3% Discount	7% Discount
MCL = 56 µg/L				
Total annual costs	$9.67	$10.28	$9.67	$10.28
Value per IQ point	$0.020	$0.004	$0.020	$0.004
Break-even avoided IQ decrements	487.53	2,674.42	487.53	2,674.42
MCL = 18 µg/L				
Total annual costs	$15.95	$16.88	$16.95	$17.96
Value per IQ point	$0.020	$0.004	$0.020	$0.004
Break-even avoided IQ decrements	803.79	4,393.37	854.23	4,674.45
Incremental between 56 and 18 µg/L				
Total annual costs	$6.28	$6.60	$7.28	$7.68
Value per IQ point	$0.00	$0.00	$0.00	$0.00
Break-even avoided IQ decrements	316.26	1,718.95	366.70	2,000.03

a. For the proposed MCL of 56 µg/L, the national estimates are the same as the estimates based on the UCMR 1 data because there were no small system sample results to extrapolate to national small system estimates. At an MCL of 18 µg/L, national estimates include extrapolation for 1 small system entry point to national estimates based on sampling weights, described above.

6.3.4 Summary of Conclusions

The analysis of costs to implement the proposed rule primarily includes administrative and monitoring costs. The Agency expects very few systems to incur treatment costs to reduce perchlorate from baseline concentrations to comply with the proposed MCL of 56 µg/L or the alternative MCL of 18 µg/L. Because the proposed rule has little impact on drinking water quality, the corresponding health risk reductions are low and estimates of benefits are more than an order of magnitude less than costs.

6.4 Effect of Uncertainties and Non-Quantified Benefit/Cost Estimates on the Estimation of National Benefits and Costs

Estimates of regulatory benefits and costs are subject to a variety of limitations such as data availability and underlying variability. Section [REF _Ref530140173 \r \h] provides an overview of several sources of uncertainty regarding the economic estimates reported above. Section [REF _Ref530140182 \r \h] recognizes that the quantitative benefits analysis is limited to a single health endpoint.

6.4.1 Summary of Major Uncertainties in the Cost and Benefit Analyses

Uncertainties regarding the economic analysis can be grouped into three general categories: baseline occurrence, benefits analysis, and cost analysis. [REF _Ref530140246 \h] characterizes the uncertainties and their potential effects on estimated costs and benefits.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Sources of Uncertainty in Economic Analysis

Description	Potential Effect[a]
Baseline occurrence	
UCMR 1 data are more than one decade old; actual occurrence could be lower (e.g., because of contaminant cleanup) or higher (e.g., because new systems use perchlorate-contaminated source water)	± (benefits and costs will change in the same direction)
UCMR 1 data include a sample of small systems; the Stage 1 results (entry point maximums) indicate that no small systems would exceed 56 µg/L and that one small system would exceed 18 µg/L; it is possible that there are additional small systems where the baseline perchlorate is greater than either MCL	− (benefits and costs will change in the same direction)
The EPA assumed a uniform distribution of system population served across the entry points; the actual entry point service population could be greater than or less than the estimates	± (benefits and costs will change in the same direction)
The EPA estimated entry point maximum concentrations using the MRL of 4 µg/L as a substitution value for nondetection sample results; the actual entry point mean concentrations could be lower	+ (benefits and costs will change in the same direction)
Benefits analysis	
The health risks and risk reductions are based on maximum recorded concentration estimates and thus do not account for exposures to concentrations greater than or less than this recorded maximum	± (benefits only)
The EPA assumed that baseline fT4 is equal to the median, which likely underestimates disease benefits as the logarithmic relationship between maternal fT4 and child IQ leads to larger relative changes in fT4, with increasing levels of perchlorate and lower levels of baseline fT4	− (benefits only)
The EPA assumed a median TSH feedback loop strength for the exposed population does not incorporate the variability in the feedback mechanism of the body's creation of TSH in response to decreasing fT4	± (benefits only)
The benefits analysis is based on a single health endpoint (see Section [REF _Ref535175449 \r \h])	− (benefits only)
Cost analysis	
The EPA assumed that systems requiring treatment would incorporate a safety factor – treating to 80% of the proposed MCL or alternative MCL, which increases costs and benefits	+ (benefits and costs will change in the same direction)
The EPA assumed that all systems requiring treatment would implement ion exchange, which may overestimate or underestimate costs	± (costs only)
The EPA developed a monitoring schedule that assumed a uniform distribution of initial monitoring costs over three years; actual costs will vary	± (costs only)
The EPA assumed that long-term monitoring costs would occur in the last year of the applicable three-year monitoring period or nine-year monitoring cycle; systems may conduct monitoring in an earlier year of the period or cycle	− (costs only)
The EPA assumed that 90% of groundwater systems and 40% of surface water systems obtained perchlorate monitoring waivers; the actual percentages may vary	± (costs only)

a. A "–" symbol indicates that benefits and/or costs will tend to be underestimated. A "+" symbol indicates that benefits and/or costs will tend to be overestimated. A "±" symbol indicates an unknown direction of uncertainty (i.e., benefits and/or costs could be underestimated or overestimated).

6.4.2 Summary of Non-Quantified Costs and Benefits

In addition to the monetized benefits, several other benefits of reducing perchlorate exposure have not been quantified. These consist of other health effects associated with perchlorate due to its alteration of iodine and thyroid hormone levels: additional neurological endpoints related maternal hypothyroxinemia such as the offspring's increased risk of schizophrenia [ADDIN

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{"citationID":"WNqAF5i1","properties":{"formattedCitation":"(Gyllenberg et al., 2016)","plainCitation":"(Gyllenberg et al., 2016)","noteIndex":0},"citationItems":[{"id":24,"uris":["http://zotero.org/groups/945096/items/937P2NGT"],"uri":["http://zotero.org/groups/945096/items/937P2NGT"],"itemData":{"id":24,"type":"article-journal","title":"Hypothyroxinemia during gestation and offspring schizophrenia in a national birth cohort","container-title":"Biological Psychiatry","page":"962-970","volume":"79","issue":"12","source":"PubMed","abstract":"BACKGROUND: Evidence from animal and human studies indicates that thyroid hormone deficiency during early gestation alters brain development. As schizophrenia is associated with prenatal brain insults and premorbid cognitive deficits, we tested the a priori hypothesis that serologically defined maternal thyroid deficiency during early gestation to mid-gestation is associated with schizophrenia in offspring.\nMETHODS: The investigation is based on the Finnish Prenatal Study of Schizophrenia, a nested case-control study that included archived maternal sera from virtually all pregnancies since 1983 (N = >1 million). We identified all offspring in the cohort with a diagnosis of schizophrenia based on the national inpatient and outpatient register and matched them on sex, date of birth, and residence in Finland at time of onset of the case to comparison subjects (1:1) from the cohort. Maternal sera of 1010 case-control pairs were assessed for free thyroxine, and sera of 948 case-control pairs were assessed for thyroid-stimulating hormone.\nRESULTS: Maternal hypothyroxinemia (free thyroxine ≤10th percentile, normal thyroid-stimulating hormone) was associated with an increased odds of schizophrenia (odds ratio = 1.75, 95% confidence interval = 1.22-2.50, p = .002). When adjusted for maternal psychiatric history, province of birth, and maternal smoking during pregnancy, the association remained significant (odds ratio = 1.70, 95% confidence interval = 1.13-2.55, p = .010).\nCONCLUSIONS: In a large, national birth cohort, prospectively documented hypothyroxinemia during early gestation to mid-gestation was associated with increased odds of schizophrenia in offspring. This information can inform translational studies of maternal hypothyroxinemia examining molecular and cellular deviations relevant to schizophrenia.","DOI":"10.1016/j.biopsych.2015.06.014","ISSN":"1873-2402","note":"PMID: 26194598\nPMCID: PMC4684794","journalAbbreviation":"Biol. Psychiatry","language":"eng","author":[{"family":"Gyllenberg","given":"David"},{"family":"Sourander","given":"Andre"},{"family":"Surcel","given":"Heljä-Marja"},{"family":"Hinkka-Yli-Salomäki","given":"Susanna"},{"family":"McKeague","given":"Ian W."},{"family":"Brown","given":"Alan S."}],"issued":{"date-parts":[["2016",6,15]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], ADHD, and expressive language delay; and CVD. Section [REF _Ref523470708 \r \h * MERGEFORMAT] provided some discussion regarding these endpoints.

Other benefits that are not associated with health risk reductions include improved perception of water quality (see Section [REF _Ref325447503 \r \h * MERGEFORMAT]) and the possibility of reducing other contaminants if perchlorate is reduced (see Section [REF _Ref325447528 \r \h * MERGEFORMAT]). Given the relatively few systems that might need to remove perchlorate, the potential benefits of these impacts are also minimal.

7 Administrative Requirements

This section provides information required by several federal statutes and Executive Orders.

7.1 Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review

Under Executive Order 12866, entitled "Regulatory Planning and Review" (58 FR 51735, October 4, 1993) and reaffirmed by Executive Order 13563, entitled "Improving Regulation and Regulatory Review" (76 FR 3821, January 21, 2011), the Agency must determine whether the regulatory action is "significant" and therefore subject to OMB review and the requirements of the Executive Order. The Order defines "significant regulatory action" as one that is likely to result in a rule that may: (1) Have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities; (2) Create a serious inconsistency or otherwise interfere with an action taken or planned by another agency; (3) Materially alter the budgetary impact of entitlements, grants, user fees, or loan programs or the rights and obligations of recipients thereof; or (4) Raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the Executive Order. Although the cost estimates in Chapter 5 do not exceed the annual cost threshold, the EPA determined that this rule is a "significant regulatory action" because it raises novel legal or policy issues. Accordingly, the EPA submitted this action to OMB for review. Changes made in response to OMB recommendations have been documented in the docket for this action.

7.2 Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted for approval to OMB under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq*. The information collection requirements are not enforceable until OMB approves them.

The information collected as a result of this rule will allow the States and the EPA to evaluate compliance with the rule. For the first 3-year period following rule promulgation, the major information requirements concern primacy agency activities to implement the rule. Compliance actions for drinking water systems (including monitoring, administration, and treatment costs) do not begin until after Year 3.

The estimate of annual average burden hours for the proposed rule during the first three years following promulgation is 48,539 hours. The annual average cost estimate is $7.4 million for labor. The burden hours per response is 2,648 hours and the cost per response is $134,154. The frequency of response (average responses per respondent) is one for primacy agencies, annually (for upfront administrative activities to implement the rule). The estimated number of likely respondents is 55 over the three year period (for an average of 18.3 each year).

Burden means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a federal agency. This includes the

time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to comply with any previously applicable instructions and requirements; train personnel to be able to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for EPA's regulations in 40 CFR are listed in 40 CFR part 9.

7.3 Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) of 1980, as amended by the Small Business Regulatory Enforcement Fairness Act (SBREFA) of 1996, generally requires an agency to prepare an initial regulatory flexibility analysis for any proposed rule subject to notice and comment rulemaking requirements under the Administrative Procedure Act or other statute unless the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Small entities include small businesses, small organizations, and small governmental jurisdictions.

For purposes of assessing the impacts of today's proposed rule on small entities, the EPA considered small entities to be public water systems serving 10,000 or fewer persons. This is the threshold specified by Congress in the 1996 Amendments to the Safe Drinking Water Act for small system flexibility provisions. In accordance with the RFA requirements, the EPA proposed using this alternative definition in the *Federal Register*, (63 FR 7620, February 13, 1998), requested public comment, consulted with the Small Business Administration (SBA), and expressed its intention to use the alternative definition for all future drinking water regulations in the Consumer Confidence Reports regulation (63 FR 44511, August 19, 1998). As stated in that final rule, the alternative definition is applied to this proposed regulation.

The proposed rule contains provisions that will affect 58,325 CWS and NTNCWS serving 10,000 or fewer people. To meet the proposed rule requirements, all of these systems will need to conduct perchlorate monitoring. At the proposed MCL of 56 µg/L, the UCMR 1 monitoring data indicate that no small systems would incur costs to reduce the levels of perchlorate in drinking water. Therefore, all small PWSs will incur monitoring costs only, as shown in [REF _Ref535312437 \h].

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Number of PWSs by Size and Ownership

Owner Type	Number of Systems			With Control Costs			Monitoring Costs Only		
	Total	Large	Small	Total	Large	Small	Total	Large	Small
Public/other[a]	30,181	3,366	26,815	2	2	0	30,179	3,364	26,815
Private	31,895	385	31,510	0	0	0	31,895	385	31,510
Total	62,076	3,751	58,325	2	2	0	62,074	3,749	58,325

a. Includes the following owner types: local, state, and federal government, Native American, public/private, and missing owner type for some NTNCWS.

Total annual monitoring and administrative costs for PWSs are approximately $6.6 million to $7.1 million annually ([REF _Ref523412826 \h]), with $5.1 million to $5.5 million accruing to small PWSs. Based on 58,325 small systems, this yields an average annual per-system cost of $88 (3% discount rate) to $94 (7% discount rate).

The EPA estimated the average annual revenues for PWSs based on the 2006 Community Water System Survey [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"WbV8Ae9u","properties":{"formattedCitation":"(USEPA, 2009c)","plainCitation":"(USEPA, 2009c)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], which includes data on revenues for private and public PWSs, and updated all values to 2017$ based on BLS [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"IadU1bbg","properties":{"formattedCitation":"(2018a)","plainCitation":"(2018a)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/E3I7HRK8"],"uri":["http://zotero.org/groups/945096/items/E3I7HRK8"],"itemData":{"id":984,"type":"article","title":"Chained consumer price index for fuels and utilities in U.S. city average, all urban consumers, 2000 to 2018","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2018"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Based on a comparison of annual costs to revenues shown in [REF _Ref535312451 \h], the EPA does not expect small entities to incur costs that exceed one percent of revenue.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Annual Monitoring and Administrative Costs as a Percentage of Average Annual Revenue for Small PWSs

Owner Type	Small Systems	Average Annual Revenues[a]	Average Annualized Costs (as a percent of revenue)	
			3% Discount	7% Discount
Local government	22,716	$1,409,252	$88 (0.006%)	$94 (0.007%)
Private	31,510	$518,439	$88 (0.017%)	$94 (0.018%)
State government	762	$1,409,252	$88 (0.006%)	$94 (0.007%)
Federal government	600	$1,409,252	$88 (0.006%)	$94 (0.007%)
Native American	751	$1,409,252	$88 (0.006%)	$94 (0.007%)
Public/private	1,825	$518,439	$88 (0.017%)	$94 (0.018%)
Unclassified	161	$518,439	$88 (0.017%)	$94 (0.018%)
Total	58,325	$838,719	$88 (0.010%)	$94 (0.010%)

a. Based on the CWSS [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZkgC4dzL","properties":{"formattedCitation":"(USEPA, 2009c Table 65)","plainCitation":"(USEPA, 2009c Table 65)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]},"suffix":"Table 65"}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and updated to 2017$ based on the chained consumer price index for fuels and utilities in U.S. city average, all urban consumers [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rkwEpGYT","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018a)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018a)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/E3I7HRK8"],"uri":["http://zotero.org/groups/945096/items/E3I7HRK8"],"itemData":{"id":984,"type":"article","title":"Chained consumer price index for fuels and utilities in U.S. city average, all urban consumers, 2000 to 2018","author":[{"literal":"Bureau of Labor Statistics (BLS)"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

7.4 Unfunded Mandates Reform Act

Title II of the Unfunded Mandates Reform Act of 1995 (UMRA), Public Law 104–4, establishes requirements for federal agencies to assess the effects of their regulatory actions on State, local, and tribal governments and the private sector. Under section 202 of UMRA, the EPA generally must prepare a written statement, including a cost-benefit analysis, for proposed and final rules with "federal mandates" that may result in expenditures to State, local, and tribal governments, in the aggregate, or to the private sector of $100 million or more in any one year, adjusted annually for inflation, or $156 million based on the most recent guidance [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"hX46uSy1","properties":{"formattedCitation":"(U.S. Department of Transportation, 2016)","plainCitation":"(U.S. Department of Transportation, 2016)","noteIndex":0},"citationItems":[{"id":1269,"uris":["http://zotero.org/groups/945096/items/GV8GHL44"],"uri":["http://zotero.org/groups/945096/items/GV8GHL44"],"itemData":{"id":1269,"type":"article","title":"Departmental Guidance: Threshold of Significant Regulatory Actions Under the Unfunded Mandates Report Act of

1995.","URL":"https://www.transportation.gov/sites/dot.gov/files/docs/Guidance%20-%20Threshold%20of%20Significant%20Regulatory%20Actions%20Under%20the%20Unfunded%20Mandates%20Reform%20Act%20of%201995.pdf","author":[{"literal":"U.S. Department of Transportation"}],"issued":{"date-parts":[["2016"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Based on the cost estimates detailed in Section [REF _Ref525051776 \r \h], the EPA determined that compliance costs in any given year will be below the threshold set in UMRA, with maximum single-year costs of approximately $16 million. The EPA has determined that this rule contains a federal mandate that will not result in expenditures of $100 million or more for State, local, and tribal governments, in the aggregate, or the private sector in any one year.

7.5 Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations

Executive Order 12898, entitled "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations" (59 FR 7629, February 16, 1994), establishes federal executive policy on environmental justice. Its main provision directs federal agencies, to the greatest extent practicable and permitted by law, to make environmental justice part of their mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental effects of their programs, policies, and activities on minority and low-income populations in the United States.

The EPA has determined that this proposed rule will not have a disproportionately high and adverse human health or environmental effects on minority or low-income populations because it increases the level considered environmental protection for all affected populations without having any disproportionately high and adverse human health or environmental effects on any population including any minority or low-income population.

7.6 Executive Order 13045: Protection of Children from Environmental Health Risks and Safety Risks

Executive Order 13045, entitled "Protection of Children from Environmental Health Risks and Safety Risks" (62 FR 19885, April 23, 1997), applies to any rule that: (1) Is determined to be "economically significant" as defined under Executive Order 12866, and (2) concerns an environmental health or safety risk that the EPA has reason to believe may have a disproportionate effect on children. If the regulatory action meets both criteria, the Agency must evaluate the environmental health or safety effects of the planned rule on children and explain why the planned regulation is preferable to other potentially effective and reasonably feasible alternatives considered by the Agency.

This proposed rule is not "economically significant" as defined under Executive Order 12866; however, the environmental health risk addressed by this action may have a disproportionate effect on children. Accordingly, and consistent with Executive Order 13045 and the EPA's Policy on Evaluating Health Risks to Children [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"H3acJl9U","properties":{"formattedCitation":"(USEPA, 2018c)","plainCitation":"(USEPA, 2018c)","noteIndex":0},"citationItems":[{"id":1256,"uris":["http://zotero.org/groups/945096/items/MADPBWYT"],"uri":["http://zotero.org/groups/945096/items/MADPBWYT"],"itemData":{"id":1256,"type":"article","title":"Memorandum: Reaffirmation of EPA's 1995 Policy on Evaluating Health Risks to Children","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], the EPA evaluated the environmental health or safety effects of perchlorate on children. The results of this evaluation are contained in the *Health Effects Technical Support Document* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"WJ6JKkg7","properties":{"formattedCitation":"(SAB and USEPA, 2013)","plainCitation":"(SAB and USEPA, 2013)","noteIndex":0},"citationItems":[{"id":1263,"uris":["http://zotero.org/groups/945096/items/3MNU7GPK"],"uri":["http://zotero.org/groups/945096/items/3MNU7GPK"],"itemData":{"id":1263,"type":"article","title":"SAB Advice on Approaches to Derive a Maximum Contaminant Level Goal for Perchlorate. EPA-SAB-13-004","author":[{"literal":"SAB"},{"family":"USEPA","given":""}],"issued":{"date-parts":[["2013"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and described in Chapter 4. The EPA has evaluated the risk associated with perchlorate in drinking water for the sensitive population – offspring of pregnant women exposed to perchlorate during the first trimester – and developed a proposed MCLG that is protective of this population as well as other children. The EPA has also estimated the health risk reduction of the proposed and alternative MCLs. This analysis is described in Chapter [REF _Ref523452255 \r \h].

7.7 Executive Order 13132: Federalism

Executive Order 13132, entitled "Federalism" (64 FR 43255, August 10, 1999) requires the EPA to develop an accountable process to ensure "meaningful and timely input by State and local officials in the development of regulatory policies that have federalism implications." "Policies that have federalism implications" is defined in the Executive Order to include regulations that have "substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government."

Under Executive Order 13132, the EPA may not issue a regulation that has federalism implications, that imposes substantial direct compliance costs, and that is not required by statute, unless the federal government provides the funds necessary to pay the direct compliance costs incurred by State and local governments, or the EPA consults with State and local officials early in the process of developing the proposed regulation.

The EPA has concluded that this proposed rule may have federalism implications, because it may impose direct compliance costs on State or local governments, and the federal government will not provide the funds necessary to pay those costs. However, the EPA estimates that the proposed rule will not result in substantial expenditures (i.e., in excess of $100 million in any one year) by State and local governments. Annual costs are estimated to range from $9.7 million

at a 3 percent discount rate to $10.3 million using a 7 percent, with $6.8 million to $7.2 million annually accruing to public entities.

7.8 Executive Order 13175: Consultation and Coordination with Indian Tribal Governments

Executive Order 13175, entitled "Consultation and Coordination with Indian Tribal Governments" (65 FR 67249, November 9, 2000) requires the EPA to develop "an accountable process to ensure meaningful and timely input by Tribal officials in the development of regulatory policies that have Tribal implications." The definition of "policies that have Tribal implications" includes regulations that have "substantial direct effects on one or more Indian tribes, on the relationship between the federal government and the Indian Tribes, or on the distribution of power and responsibilities between the Federal government and Indian Tribes." Under Executive Order 13175, the EPA may not issue a regulation that has Tribal implications, that imposes substantial direct compliance costs, and that is not required by statute, unless the federal government provides the funds necessary to pay the direct compliance costs incurred by Tribal governments, or the EPA consults with Tribal officials early in the process of developing the proposed regulation and develops a Tribal summary impact statement.

The EPA has concluded that this proposed rule may have Tribal implications, because it may impose direct compliance costs on Tribal governments, and the federal government will not provide the funds necessary to pay those costs. The EPA has identified 768 water systems with 1,167 entry points under Native American ownership that may be subject to the proposed rule. They will bear an estimated total annualized cost of $74,095 at a 3 percent discount rate ($79,620 at 7 percent) to implement this rule as proposed, with all costs attributable to monitoring and administrative costs. Estimated average annualized cost per system ranges from $96 at a 3 percent discount rate to $104 at a 7 percent discount rate.

Accordingly, the EPA provides the following Tribal summary impact statement as required by section 5(b) of Executive Order 13175. The EPA consulted with representatives of Tribal officials early in the process of developing this proposed regulation to permit them to have meaningful and timely input into its development. The EPA conducted consultation with Indian Tribes, which included a public meeting in February 28, 2012, to request input and provide rulemaking information to interested parties. A meeting summary report is available on the docket for public inspection (USEPA, 2012). The EPA notes that 751 of the 768 Tribal systems identified by the Agency as subject to the proposed rule are small systems that are expected to incur only monitoring costs. Due to the health risks associated with perchlorate, capital expenditures needed for compliance with the rule will be eligible for federal funding sources, specifically the Drinking Water State Revolving Fund. In the spirit of Executive Order 13175, and consistent with the EPA's policy to promote communications between the EPA and Tribal governments, the EPA specifically solicits additional comment on this proposed rule from Tribal officials.

7.9 Executive Order 13211: Actions Concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use

This rule is not a "significant energy action" as defined in Executive Order 13211, entitled "Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use" (66 FR 28355, May 22, 2001), because it is not likely to have a significant adverse effect on the supply, distribution, or use of energy. This determination is based on the following analysis.

The first consideration is whether the proposed rule would adversely affect the supply of energy. The proposed rule does not regulate power generation, either directly or indirectly. The public and private water systems that the proposed rule regulates do not generate power. Further, the cost increases borne by customers of water utilities as a result of the proposed rule are a low percentage of the total cost of water, except for a few water systems that might install treatment technologies and would likely spread that cost over their customer base. In sum, the proposed rule does not regulate the supply of energy, does not generally regulate the utilities that supply energy, and is unlikely to affect significantly the customer base of energy suppliers. Thus, the proposed rule would not translate into adverse effects on the supply of energy.

The second consideration is whether the proposed rule would adversely affect the distribution of energy. The proposed rule does not regulate any aspect of energy distribution. The water systems that are regulated by the proposed rule already have electrical service. At the proposed MCL, one entry point at one system may require incremental power to operate new treatment processes. The increase in peak electricity demand at water utilities is negligible. Therefore, the EPA estimates that the existing connections are adequate and that the proposed rule has no discernable adverse effect on energy distribution.

The third consideration is whether the proposed rule would adversely affect the use of energy. Because only one system is expected to add treatment technologies that use electrical power, this potential impact on sector demand or overall national demand for power is negligible.

Based on its analysis of these considerations, the EPA has concluded that proposed rule is not likely to have a significant adverse effect on the supply, distribution, or use of energy.

7.10 National Technology Transfer and Advancement Act of 1995

Section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA), Public Law 104–113, 12(d) (15 U.S.C. 272 note) directs the EPA to use voluntary consensus standards in its regulatory activities unless to do so would be inconsistent with applicable law or otherwise impractical. Voluntary consensus standards are technical standards (e.g., materials specifications, test methods, sampling procedures, and business practices) that are developed or adopted by voluntary consensus standards bodies. The NTTAA directs the EPA to provide Congress, through OMB, explanations when the Agency decides not to use available and applicable voluntary consensus standards. The proposed rulemaking involves technical standards. The proposed rule could involve voluntary consensus standards in that it would require monitoring for perchlorate. The EPA proposed five analytical methods for the identification and quantification of perchlorate in drinking water. EPA methods 314.0, 314.1,

314.2, 331.0, and 332.0 incorporate quality control criteria that allow accurate quantitation of perchlorate.

The EPA's monitoring and sampling protocols generally include voluntary consensus standards developed by agencies such as ASTM International, Standard Methods and other such bodies wherever the EPA deems these methodologies appropriate for compliance monitoring.

7.11 Impacts on Sensitive Subpopulations and Life Stages

Section 1412(b)(3)(C)(i) of the SDWA requires that the EPA evaluate the effects of a contaminant on the general population and on potentially sensitive subpopulations such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other sub-populations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population. For the proposed perchlorate rule, the EPA based the proposed MCLG and the benefits analysis in Chapter 4 on a sensitive life stage – the offspring of pregnant women exposed to perchlorate during their first trimester. The Agency determined that an MCLG protective of this sensitive life stage would also be protective of other sensitive life stages. See Chapter 4 for a discussion of the MCLG development method.

7.12 Consultations with the Science Advisory Board, National Drinking Water Advisory Council, and the Secretary of Health and Human Services

In accordance with sections 1412 (d) and 1412 (e) of the SDWA, the Agency consulted with the National Drinking Water Advisory Council (NDWAC or the Council); the Secretary of Health and Human Services (HHS); and with the EPA SAB. The Agency consulted with NDWAC during the Council's October 4-5, 2012 meeting. A summary of the NDWAC recommendations is available in the Fall 2012 Meeting Summary Report [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mQCvFjdz","properties":{"formattedCitation":"(NDWAC, 2012)","plainCitation":"(NDWAC, 2012)","noteIndex":0},"citationItems":[{"id":1268,"uris":["http://zotero.org/groups/945096/items/UIZPA9CD"],"uri":["http://zotero.org/groups/945096/items/UIZPA9CD"],"itemData":{"id":1268,"type":"article","title":"Meeting Summary, October 4-5, 2012.","URL":"https://www.epa.gov/sites/production/files/2015-10/documents/3ndwac2012oct4-5summary.pdf","author":[{"literal":"NDWAC"}],"issued":{"date-parts":[["2012"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and the docket for this proposed rule. The EPA carefully considered NDWAC recommendations during development of a proposed drinking water rule for perchlorate.

On May 29, 2012, the EPA sought guidance from the EPA SAB on how best to consider and interpret life stage information, epidemiological and biomonitoring data since the publication of the National Research Council 2005 report, the Agency's PBPK analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"b0Nazc6r","properties":{"formattedCitation":"(NRC, 2005;

USEPA, 2012)","plainCitation":"(NRC, 2005; USEPA,
2012)","noteIndex":0},"citationItems":[{"id":349,"uris":["http://zotero.org/groups/945096/items/
TN6HMC9D"],"uri":["http://zotero.org/groups/945096/items/TN6HMC9D"],"itemData":{"id":3
49,"type":"book","title":"Health Implications of Perchlorate Ingestion","publisher":"National
Academies Press","publisher-place":"Washington, DC","event-place":"Washington,
DC","author":[{"literal":"NRC"}],"issued":{"date-
parts":[["2005"]]}}},{"id":1088,"uris":["http://zotero.org/groups/945096/items/WS4SC2GM"],"
uri":["http://zotero.org/groups/945096/items/WS4SC2GM"],"itemData":{"id":1088,"type":"articl
e","title":"Benchmark dose technical guidance","author":[{"literal":"USEPA"}],"issued":{"date-
parts":[["2012"]]}}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}]. On May 29, 2013, the EPA received
significant input from SAB, summarized in the report, *SAB Advice on Approaches to Derive a
Maximum Contaminant Level Goal for Perchlorate*[ADDIN ZOTERO_ITEM CSL_CITATION
{"citationID":"pq8BBx4X","properties":{"formattedCitation":"(USEPA,
2013)","plainCitation":"(USEPA,
2013)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1263,"uris":["http://zotero.org/g
roups/945096/items/3MNU7GPK"],"uri":["http://zotero.org/groups/945096/items/3MNU7GPK"
],"itemData":{"id":1263,"type":"article","title":"SAB Advice on Approaches to Derive a
Maximum Contaminant Level Goal for Perchlorate. EPA-SAB-13-
004","author":[{"literal":"SAB"},{"family":"USEPA","given":""}],"issued":{"date-
parts":[["2013"]]}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}] [ADDIN ZOTERO_ITEM CSL_CITATION
{"citationID":"BQIl5FgF","properties":{"formattedCitation":"(SAB and USEPA,
2013)","plainCitation":"(SAB and USEPA,
2013)","noteIndex":0},"citationItems":[{"id":1263,"uris":["http://zotero.org/groups/945096/item
s/3MNU7GPK"],"uri":["http://zotero.org/groups/945096/items/3MNU7GPK"],"itemData":{"id":
1263,"type":"article","title":"SAB Advice on Approaches to Derive a Maximum Contaminant
Level Goal for Perchlorate. EPA-SAB-13-
004","author":[{"literal":"SAB"},{"family":"USEPA","given":""}],"issued":{"date-
parts":[["2013"]]}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}].

On July 15, 2013, the EPA responded by stating that the Agency would consider all the recommendations from the SAB, as it continued working on the development of the rulemaking process for perchlorate (USEPA, 2013). To address SAB recommendations, the EPA collaborated with Food and Drug Administration (FDA) scientists to develop PBPK/PD, or BBDR, models that incorporate all available health-related information on perchlorate to predict changes in thyroid hormones in a sensitive life stages exposed to different dietary iodide and perchlorate levels [ADDIN ZOTERO_ITEM CSL_CITATION
{"citationID":"yl7M4vOP","properties":{"formattedCitation":"(USEPA,
2017a)","plainCitation":"(USEPA,
2017a)","noteIndex":0},"citationItems":[{"id":50,"uris":["http://zotero.org/groups/945096/items/
NH2URBTL"],"uri":["http://zotero.org/groups/945096/items/NH2URBTL"],"itemData":{"id":50
,"type":"report","title":"Draft Report: Proposed Approaches to Inform the Derivation of a
Maximum Contaminant Level Goal for Perchlorate in Drinking
Water","author":[{"literal":"USEPA"}],"issued":{"date-
parts":[["2017",9]]}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}]. As recommended by SAB, the EPA developed these models based upon perchlorate's MOA (i.e., iodide uptake inhibition by the thyroid; USEPA, 2013). Additional details are in the *Health Effects Technical Support Document* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"LfAWm4FT","properties":{"formattedCitation":"(USEPA, 2018b)","plainCitation":"(USEPA, 2018b)","noteIndex":0},"citationItems":[{"id":1201,"uris":["http://zotero.org/groups/945096/items/MT6BJDE3"],"uri":["http://zotero.org/groups/945096/items/MT6BJDE3"],"itemData":{"id":1201,"type":"report","title":"Health Effects Technical Support Document","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and described above in chapter 4.

In accordance with SAB recommendations, the EPA developed a two-stage approach to integrate BBDR model results with data on neurodevelopmental outcomes from epidemiological studies, this approach allowed the Agency to link maternal thyroid hormones levels as a result of low iodine and perchlorate exposure, to derive an MCLG that directly addresses the most sensitive life stage (USEPA, 2013).

On [INSERT DATE], the EPA consulted with the HHS. The EPA received a favorable response to the Agency's novel approach and development of the proposed MCLG, no objection was raised as a result of the consultation.

7.13 Technical, Financial, and Managerial Capacity of Public Water Systems

The EPA considered whether the regulated CWS and NTNCWS would have the technical, financial, and managerial capacity to implement the proposed rule as required by Section 1420(d)(3) of the SDWA. Because the vast majority of the systems would only be required to conduct periodic monitoring for perchlorate, the Agency determined that the affected systems should have the capacity to comply with the rule. Very few systems are expected to require additional treatment to meet the proposed MCL. All of these systems are large systems, which are more likely than small systems to have the capacity to implement treatment.

7.14 National Affordability Determination

The EPA determined that there are several affordable treatment technologies for small systems. The determination, documented in *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"JNSHWgHz","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1189,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1189,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}], compared the estimated incremental treatment costs per household with a baseline expenditure margin that equals 2.5 percent of median household income minus baseline drinking water utility per household. [REF _Ref535312503 \h] shows which technologies satisfy the affordability criterion for three small system size categories. For the smallest system size category, ion exchange and point-of-use reverse osmosis are affordable technologies, but biological treatment and centralized reverse osmosis are not.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Proposed Small System Compliance Technologies for Perchlorate Removal

System Size (population served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25–500	Yes	No	No	Yes
501–3,300	Yes	Yes	Yes	Yes
3,301–10,000	Yes	Yes	Yes	Not applicable[a]

a. EPA's WBS cost model for POU treatment does not cover systems larger than 3,300 people (greater than 1 MGD design flow).because implementing and maintaining a large-scale POU program in lieu of central treatment for perchlorate is likely to be impractical.

The small system compliance technology (SSCT) listed in [REF _Ref532979324 \h] include a POU version of reverse osmosis. Although this technology is not a proposed BAT, it can meet the proposed MCL and, therefore, meets the effectiveness requirement for an SSCT. For perchlorate removal, the NSF Joint Committee on Drinking Water Treatment Units added a protocol to NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems that requires a reverse osmosis unit to be able to reduce perchlorate from a challenge level of 130 µg/L to a target level of 4 µg/L [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NYqGuVQI","properties":{"formattedCitation":"(NSF International, 2004)","plainCitation":"(NSF International, 2004)","noteIndex":0},"citationItems":[{"id":997,"uris":["http://zotero.org/groups/945096/items/9EAEK7S4"],"uri":["http://zotero.org/groups/945096/items/9EAEK7S4"],"itemData":{"id":997,"type":"webpage","title":"Perchlorate Reduction","URL":"http://www.nsf.org/consumer/drinking_water/perchlorate_reduction.asp","author":[{"literal":"NSF International"}],"issued":{"date-parts":[["2004"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Organizations (e.g., NSF International, Underwriters Laboratories, Water Quality Association) provide third-party testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media.

The operating principle for POU reverse osmosis devices is the same as centralized reverse osmosis: steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to a reverse osmosis membrane for dissolved ion removal, POU reverse osmosis devices often have a sediment pre-filter and a carbon filter in front of the reverse osmosis membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

The EPA identified the SSCT using the affordability criteria it developed for drinking water rules [ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"LHgBHn5b","properties":{"formattedCitation":"(USEPA, 1998)","plainCitation":"(USEPA, 1998)","noteIndex":0},"citationItems":[{"id":1215,"uris":["http://zotero.org/groups/945096/items/399QNBY4"],"uri":["http://zotero.org/groups/945096/items/399QNBY4"],"itemData":{"id":1215,"type":"article","title":"Variance Technology Findings for Contaminants Regulated Before 1996","publisher":"EPA 815–R– 98–003. September","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["1998"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The analysis method is a comparison of estimated incremental household costs for perchlorate treatment to an expenditure margin, which is the difference between baseline household water costs and a threshold equal to 2.5 percent of median household income. [REF _Ref535312582 \h] shows the expenditure margins derived for the analysis.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Expenditure Margins for SSCT Affordability Analysis

System Size (population served)	Median Household Income[a] (a)	Affordability Threshold[b] (b) = 2.5% x a	Baseline Water Cost[c] (c)	Expenditure Margin (d) = b - c
25-500	$52,791	$1,320	$341	$979
501-3,300	$51,093	$1,277	$395	$883
3,301-10,000	$55,975	$1,399	$412	$987

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2scXqyv0","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1189,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1189,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

a. Mean household income (MHI) is based on U.S. Census 2010 ACS 5-year estimates [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"x096Tc8Y","properties":{"formattedCitation":"(U.S. Census Bureau, 2010)","plainCitation":"(U.S. Census Bureau, 2010)","noteIndex":0},"citationItems":[{"id":1225,"uris":["http://zotero.org/groups/945096/items/WJ35QNBT"],"uri":["http://zotero.org/groups/945096/items/WJ35QNBT"],"itemData":{"id":1225,"type":"article","title":"American Community Survey, 5-year Estimates (2006-2010)","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2010"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] stated in 2010 dollars, adjusted to 2017 dollars using the CPI (for all items) for areas under 50,000 persons [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7Rg9m81J","properties":{"formattedCitation":"(Bureau of Labor Statistics (BLS), 2018b)","plainCitation":"(Bureau of Labor Statistics (BLS), 2018b)","noteIndex":0},"citationItems":[{"id":1218,"uris":["http://zotero.org/groups/945096/items/GTI7H6YK"],"uri":["http://zotero.org/groups/945096/items/GTI7H6YK"],"itemData":{"id":1218,"type":"article","title":"CPI--All Urban Consumers (all items), for areas under 50,000 persons","author":[{"family":"Bureau of Labor Statistics (BLS)","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

b. Affordability threshold equals 2.5 percent of MHI.

c. Household water costs derived from 2006 Community Water System Survey [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"fS2Ibu6t","properties":{"formattedCitation":"(USEPA, 2009c)","plainCitation":"(USEPA, 2009c)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], based on residential revenue per connection within each size category, adjusted to 2017 dollars based on the CPI (for all items) for areas under 50,000 persons.

[REF _Ref535312595 \h] shows the estimates of per-household costs by treatment technology and size category generated using the treatment cost method described in section XI.B as well as *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"z6GYvRh1","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1189,"uris":["http://zotero.org/groups/945096/ite

ms/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1189,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] and *Technologies and Costs for Treating Perchlorate-Contaminated Waters* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"18aKvRLD","properties":{"formattedCitation":"(USEPA, 2018g)","plainCitation":"(USEPA, 2018g)","noteIndex":0},"citationItems":[{"id":977,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":977,"type":"report","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Costs in bold font do not exceed the corresponding expenditure margin and, therefore, meet the SSCT affordability criterion.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]: Annual Incremental Cost Estimates for SSCT Affordability Analysis

System Size (population served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25–500	**$378 to $610**	$2,146 to $3,709	$2,272 to $2,671	**$265 to $271**
501–3,300	**$98 to $148**	**$324 to $566**	**$561 to $688**	**$250 to $251**
3,301–10,000	**$104 to $153**	**$211 to $315**	**$431 to $493**	Not applicable[a]

Source: *Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8y1WSJT4","properties":{"formattedCitation":"(USEPA, 2018a)","plainCitation":"(USEPA, 2018a)","noteIndex":0},"citationItems":[{"id":1189,"uris":["http://zotero.org/groups/945096/items/QBLZF9AR"],"uri":["http://zotero.org/groups/945096/items/QBLZF9AR"],"itemData":{"id":1189,"type":"article","title":"Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water.","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]; bold font indicates cost estimates that do not exceed the corresponding expenditure margin.

a. EPA's WBS model for POU treatment does not cover systems larger than 3,300 people (greater than 1 MGD design flow), because implementing and maintaining a large-scale POU program is likely to be impractical.

8 References

[ADDIN ZOTERO_BIBL {"uncited":[],"omitted":[],"custom":[]} CSL_BIBLIOGRAPHY]

Appendix A. Output from the BBDR Model Summarizing Maternal fT4 Levels Given Increasing Dose of Perchlorate

Perchlorate Dose (µg/kg/day)	Iodine Intake Levels; fT4 (pmol/L)														
	50	55	60	65	70	75	80	85	90	95	100	125	150	170	300
0	8.27	8.47	8.67	8.87	9.06	9.26	9.47	9.67	9.87	10.05	10.18	10.40	10.47	10.50	10.57
0.1	8.27	8.47	8.66	8.86	9.06	9.26	9.46	9.67	9.87	10.04	10.17	10.40	10.47	10.50	10.57
0.2	8.26	8.46	8.66	8.86	9.05	9.25	9.46	9.66	9.86	10.04	10.17	10.40	10.47	10.50	10.57
0.3	8.26	8.46	8.66	8.85	9.05	9.25	9.45	9.65	9.85	10.03	10.17	10.40	10.46	10.50	10.57
0.4	8.26	8.46	8.65	8.85	9.04	9.24	9.45	9.65	9.85	10.03	10.16	10.40	10.46	10.50	10.57
0.5	8.25	8.45	8.65	8.84	9.04	9.24	9.44	9.64	9.84	10.02	10.16	10.40	10.46	10.50	10.57
0.6	8.25	8.45	8.65	8.84	9.04	9.23	9.43	9.64	9.84	10.02	10.15	10.40	10.46	10.50	10.57
0.7	8.25	8.45	8.64	8.84	9.03	9.23	9.43	9.63	9.83	10.01	10.15	10.39	10.46	10.50	10.57
0.8	8.24	8.44	8.64	8.83	9.03	9.22	9.42	9.63	9.82	10.00	10.15	10.39	10.46	10.50	10.57
0.9	8.24	8.44	8.64	8.83	9.02	9.22	9.42	9.62	9.82	10.00	10.14	10.39	10.46	10.50	10.57
1	8.24	8.44	8.63	8.82	9.02	9.21	9.41	9.61	9.81	9.99	10.14	10.39	10.46	10.50	10.57
1.1	8.24	8.43	8.63	8.82	9.01	9.21	9.41	9.61	9.81	9.99	10.13	10.39	10.46	10.49	10.57
1.2	8.23	8.43	8.62	8.82	9.01	9.20	9.40	9.60	9.80	9.98	10.13	10.39	10.46	10.49	10.57
1.3	8.23	8.43	8.62	8.81	9.00	9.20	9.40	9.60	9.79	9.98	10.13	10.39	10.46	10.49	10.57
1.4	8.23	8.42	8.62	8.81	9.00	9.19	9.39	9.59	9.79	9.97	10.12	10.39	10.46	10.49	10.57
1.5	8.22	8.42	8.61	8.80	9.00	9.19	9.39	9.58	9.78	9.97	10.12	10.39	10.46	10.49	10.57
1.6	8.22	8.42	8.61	8.80	8.99	9.18	9.38	9.58	9.78	9.96	10.11	10.39	10.46	10.49	10.57
1.7	8.22	8.42	8.61	8.80	8.99	9.18	9.38	9.57	9.77	9.96	10.11	10.39	10.46	10.49	10.57
1.8	8.22	8.41	8.60	8.79	8.98	9.17	9.37	9.57	9.76	9.95	10.10	10.39	10.46	10.49	10.57
1.9	8.21	8.41	8.60	8.79	8.98	9.17	9.36	9.56	9.76	9.94	10.10	10.38	10.46	10.49	10.57
2	8.21	8.41	8.60	8.79	8.97	9.17	9.36	9.56	9.75	9.94	10.09	10.38	10.46	10.49	10.57
2.1	8.21	8.40	8.59	8.78	8.97	9.16	9.35	9.55	9.75	9.93	10.09	10.38	10.46	10.49	10.57
2.2	8.20	8.40	8.59	8.78	8.97	9.16	9.35	9.55	9.74	9.93	10.08	10.38	10.46	10.49	10.57
2.3	8.20	8.40	8.59	8.77	8.96	9.15	9.34	9.54	9.74	9.92	10.08	10.38	10.46	10.49	10.57
2.4	8.20	8.39	8.58	8.77	8.96	9.15	9.34	9.53	9.73	9.92	10.08	10.38	10.45	10.49	10.57
2.5	8.20	8.39	8.58	8.77	8.95	9.14	9.33	9.53	9.72	9.91	10.07	10.38	10.45	10.49	10.57

Perchlorate Dose (µg/kg/day)	Iodine Intake Levels; fT4 (pmol/L)														
	50	55	60	65	70	75	80	85	90	95	100	125	150	170	300
2.6	8.19	8.39	8.58	8.76	8.95	9.14	9.33	9.52	9.72	9.90	10.07	10.38	10.45	10.49	10.57
2.7	8.19	8.38	8.57	8.76	8.95	9.13	9.32	9.52	9.71	9.90	10.06	10.38	10.45	10.49	10.57
2.8	8.19	8.38	8.57	8.76	8.94	9.13	9.32	9.51	9.71	9.89	10.06	10.38	10.45	10.49	10.57
2.9	8.19	8.38	8.57	8.75	8.94	9.12	9.31	9.51	9.70	9.89	10.05	10.38	10.45	10.49	10.57
3	8.18	8.38	8.56	8.75	8.93	9.12	9.31	9.50	9.70	9.88	10.05	10.37	10.45	10.49	10.57
3.1	8.18	8.37	8.56	8.74	8.93	9.12	9.30	9.50	9.69	9.88	10.04	10.37	10.45	10.49	10.57
3.2	8.18	8.37	8.56	8.74	8.92	9.11	9.30	9.49	9.68	9.87	10.04	10.37	10.45	10.49	10.57
3.3	8.17	8.37	8.55	8.74	8.92	9.11	9.29	9.49	9.68	9.87	10.03	10.37	10.45	10.49	10.57
3.4	8.17	8.36	8.55	8.73	8.92	9.10	9.29	9.48	9.67	9.86	10.03	10.37	10.45	10.49	10.57
3.5	8.17	8.36	8.55	8.73	8.91	9.10	9.29	9.48	9.67	9.85	10.02	10.37	10.45	10.49	10.57
3.6	8.17	8.36	8.54	8.73	8.91	9.09	9.28	9.47	9.66	9.85	10.02	10.37	10.45	10.49	10.57
3.7	8.16	8.35	8.54	8.72	8.90	9.09	9.28	9.47	9.66	9.84	10.01	10.37	10.45	10.49	10.57
3.8	8.16	8.35	8.54	8.72	8.90	9.08	9.27	9.46	9.65	9.84	10.01	10.37	10.45	10.48	10.57
3.9	8.16	8.35	8.53	8.72	8.90	9.08	9.27	9.45	9.64	9.83	10.00	10.37	10.45	10.48	10.57
4	8.16	8.35	8.53	8.71	8.89	9.08	9.26	9.45	9.64	9.83	10.00	10.36	10.45	10.48	10.57
4.1	8.15	8.34	8.53	8.71	8.89	9.07	9.26	9.44	9.63	9.82	9.99	10.36	10.45	10.48	10.57
4.2	8.15	8.34	8.52	8.70	8.89	9.07	9.25	9.44	9.63	9.81	9.99	10.36	10.45	10.48	10.57
4.3	8.15	8.34	8.52	8.70	8.88	9.06	9.25	9.43	9.62	9.81	9.98	10.36	10.45	10.48	10.57
4.4	8.14	8.33	8.52	8.70	8.88	9.06	9.24	9.43	9.62	9.80	9.98	10.36	10.45	10.48	10.57
4.5	8.14	8.33	8.51	8.69	8.87	9.05	9.24	9.42	9.61	9.80	9.97	10.36	10.44	10.48	10.57
4.6	8.14	8.33	8.51	8.69	8.87	9.05	9.23	9.42	9.61	9.79	9.97	10.36	10.44	10.48	10.57
4.7	8.14	8.33	8.51	8.69	8.87	9.05	9.23	9.41	9.60	9.79	9.96	10.36	10.44	10.48	10.57
4.8	8.13	8.32	8.51	8.68	8.86	9.04	9.22	9.41	9.60	9.78	9.95	10.36	10.44	10.48	10.57
4.9	8.13	8.32	8.50	8.68	8.86	9.04	9.22	9.40	9.59	9.78	9.95	10.35	10.44	10.48	10.57
5	8.13	8.32	8.50	8.68	8.86	9.03	9.22	9.40	9.59	9.77	9.94	10.35	10.44	10.48	10.57
5.1	8.13	8.31	8.50	8.67	8.85	9.03	9.21	9.39	9.58	9.76	9.94	10.35	10.44	10.48	10.57
5.2	8.12	8.31	8.49	8.67	8.85	9.03	9.21	9.39	9.57	9.76	9.93	10.35	10.44	10.48	10.57
5.3	8.12	8.31	8.49	8.67	8.84	9.02	9.20	9.38	9.57	9.75	9.93	10.35	10.44	10.48	10.57
5.4	8.12	8.31	8.49	8.66	8.84	9.02	9.20	9.38	9.56	9.75	9.92	10.35	10.44	10.48	10.57

Perchlorate Dose (µg/kg/day)	Iodine Intake Levels; fT4 (pmol/L)														
	50	55	60	65	70	75	80	85	90	95	100	125	150	170	300
5.5	8.12	8.30	8.48	8.66	8.84	9.01	9.19	9.37	9.56	9.74	9.92	10.35	10.44	10.48	10.57
5.6	8.11	8.30	8.48	8.66	8.83	9.01	9.19	9.37	9.55	9.74	9.91	10.35	10.44	10.48	10.57
5.7	8.11	8.30	8.48	8.65	8.83	9.01	9.18	9.36	9.55	9.73	9.91	10.35	10.44	10.48	10.57
5.8	8.11	8.30	8.47	8.65	8.83	9.00	9.18	9.36	9.54	9.73	9.90	10.34	10.44	10.48	10.57
5.9	8.11	8.29	8.47	8.65	8.82	9.00	9.18	9.36	9.54	9.72	9.90	10.34	10.44	10.48	10.57
6	8.10	8.29	8.47	8.64	8.82	8.99	9.17	9.35	9.53	9.72	9.89	10.34	10.44	10.48	10.57
6.1	8.10	8.29	8.47	8.64	8.81	8.99	9.17	9.35	9.53	9.71	9.89	10.34	10.44	10.48	10.57
6.2	8.10	8.28	8.46	8.64	8.81	8.99	9.16	9.34	9.52	9.70	9.88	10.34	10.44	10.48	10.57
6.3	8.10	8.28	8.46	8.63	8.81	8.98	9.16	9.34	9.52	9.70	9.88	10.34	10.44	10.48	10.56
6.4	8.09	8.28	8.46	8.63	8.80	8.98	9.15	9.33	9.51	9.69	9.87	10.34	10.43	10.47	10.56
6.5	8.09	8.28	8.45	8.63	8.80	8.97	9.15	9.33	9.51	9.69	9.86	10.34	10.43	10.47	10.56
6.6	8.09	8.27	8.45	8.62	8.80	8.97	9.15	9.32	9.50	9.68	9.86	10.33	10.43	10.47	10.56
6.7	8.09	8.27	8.45	8.62	8.79	8.97	9.14	9.32	9.50	9.68	9.85	10.33	10.43	10.47	10.56
6.8	8.08	8.27	8.45	8.62	8.79	8.96	9.14	9.31	9.49	9.67	9.85	10.33	10.43	10.47	10.56
6.9	8.08	8.27	8.44	8.62	8.79	8.96	9.13	9.31	9.49	9.67	9.84	10.33	10.43	10.47	10.56
7	8.08	8.26	8.44	8.61	8.78	8.95	9.13	9.30	9.48	9.66	9.84	10.33	10.43	10.47	10.56
7.1	8.08	8.26	8.44	8.61	8.78	8.95	9.12	9.30	9.48	9.66	9.83	10.33	10.43	10.47	10.56
7.2	8.07	8.26	8.43	8.61	8.78	8.95	9.12	9.30	9.47	9.65	9.83	10.33	10.43	10.47	10.56
7.3	8.07	8.26	8.43	8.60	8.77	8.94	9.12	9.29	9.47	9.65	9.82	10.32	10.43	10.47	10.56
7.4	8.07	8.25	8.43	8.60	8.77	8.94	9.11	9.29	9.46	9.64	9.82	10.32	10.43	10.47	10.56
7.5	8.07	8.25	8.43	8.60	8.77	8.94	9.11	9.28	9.46	9.64	9.81	10.32	10.43	10.47	10.56
7.6	8.07	8.25	8.42	8.59	8.76	8.93	9.10	9.28	9.45	9.63	9.81	10.32	10.43	10.47	10.56
7.7	8.06	8.24	8.42	8.59	8.76	8.93	9.10	9.27	9.45	9.63	9.80	10.32	10.43	10.47	10.56
7.8	8.06	8.24	8.42	8.59	8.76	8.93	9.10	9.27	9.44	9.62	9.80	10.32	10.43	10.47	10.56
7.9	8.06	8.24	8.41	8.58	8.75	8.92	9.09	9.26	9.44	9.62	9.79	10.32	10.43	10.47	10.56
8	8.06	8.24	8.41	8.58	8.75	8.92	9.09	9.26	9.43	9.61	9.79	10.31	10.43	10.47	10.56
8.1	8.05	8.23	8.41	8.58	8.75	8.91	9.08	9.26	9.43	9.61	9.78	10.31	10.42	10.47	10.56
8.2	8.05	8.23	8.41	8.58	8.74	8.91	9.08	9.25	9.42	9.60	9.78	10.31	10.42	10.47	10.56
8.3	8.05	8.23	8.40	8.57	8.74	8.91	9.08	9.25	9.42	9.60	9.77	10.31	10.42	10.47	10.56

Perchlorate Dose (µg/kg/day)	Iodine Intake Levels; fT4 (pmol/L)														
	50	55	60	65	70	75	80	85	90	95	100	125	150	170	300
8.4	8.05	8.23	8.40	8.57	8.74	8.90	9.07	9.24	9.42	9.59	9.76	10.31	10.42	10.47	10.56
8.5	8.04	8.22	8.40	8.57	8.73	8.90	9.07	9.24	9.41	9.59	9.76	10.31	10.42	10.47	10.56
8.6	8.04	8.22	8.39	8.56	8.73	8.90	9.06	9.23	9.41	9.58	9.75	10.30	10.42	10.47	10.56
8.7	8.04	8.22	8.39	8.56	8.73	8.89	9.06	9.23	9.40	9.58	9.75	10.30	10.42	10.47	10.56
8.8	8.04	8.22	8.39	8.56	8.72	8.89	9.06	9.23	9.40	9.57	9.74	10.30	10.42	10.46	10.56
8.9	8.04	8.21	8.39	8.55	8.72	8.89	9.05	9.22	9.39	9.57	9.74	10.30	10.42	10.46	10.56
9	8.03	8.21	8.38	8.55	8.72	8.88	9.05	9.22	9.39	9.56	9.73	10.30	10.42	10.46	10.56
9.1	8.03	8.21	8.38	8.55	8.71	8.88	9.04	9.21	9.38	9.56	9.73	10.30	10.42	10.46	10.56
9.2	8.03	8.21	8.38	8.55	8.71	8.87	9.04	9.21	9.38	9.55	9.72	10.29	10.42	10.46	10.56
9.3	8.03	8.20	8.38	8.54	8.71	8.87	9.04	9.20	9.37	9.55	9.72	10.29	10.42	10.46	10.56
9.4	8.02	8.20	8.37	8.54	8.70	8.87	9.03	9.20	9.37	9.54	9.71	10.29	10.42	10.46	10.56
9.5	8.02	8.20	8.37	8.54	8.70	8.86	9.03	9.20	9.37	9.54	9.71	10.29	10.42	10.46	10.56
9.6	8.02	8.20	8.37	8.53	8.70	8.86	9.03	9.19	9.36	9.53	9.70	10.29	10.42	10.46	10.56
9.7	8.02	8.19	8.37	8.53	8.69	8.86	9.02	9.19	9.36	9.53	9.70	10.29	10.42	10.46	10.56
9.8	8.01	8.19	8.36	8.53	8.69	8.85	9.02	9.18	9.35	9.52	9.69	10.28	10.41	10.46	10.56
9.9	8.01	8.19	8.36	8.53	8.69	8.85	9.01	9.18	9.35	9.52	9.69	10.28	10.41	10.46	10.56
10	8.01	8.19	8.36	8.52	8.69	8.85	9.01	9.18	9.34	9.51	9.68	10.28	10.41	10.46	10.56

Appendix B. Estimated Value of an IQ Point

Valuing changes in the intelligence quotient (IQ) is an important component to monetizing the effects of regulations expected to have significant impacts on IQ. The dollar value of a single IQ point is often equated to the change in lifetime earnings associated with an additional IQ point. This appendix describes the method used to estimate the average lifetime earnings of an individual born into a particular birth cohort and the associated effect of a one point change in IQ.

[REF _Ref532978150 \h] summarizes this appendix's estimates of the IQ point dollar values produced in 2017 dollars. The values can be used to estimate the benefits of avoiding IQ decrements.

Exhibit [STYLEREF 5 \s]-[SEQ Table * ARABIC \s 5]: Summary of IQ Point Dollar Values (2017$)

Estimate Parameter	Discount Rate	
	3%	7%
IQ value	$23,269	$5,398
Additional education costs and lost earnings	$1,592	$691
IQ value without additional education costs and lost earnings	$21,677	$4,707

[REF _Ref532978235 \h] presents a summary of the changes incorporated into the method used in this analysis compared to methods used in previous EPA analyses. In addition to relying on more recent data, this analysis incorporates several methodological changes designed to improve the estimates for the value of an IQ point.

Exhibit [STYLEREF 5 \s]-[SEQ Table * ARABIC \s 5]: Difference between the Current Methods and Previous Methods Used to Estimate Lifetime Earnings

Data and methods	Uses the average of ten ACS single-year Public Use Microdata Sample (PUMS; 2008 to 2017) in place of a single cross-section of the Current Population Survey (CPS). The ACS has a larger sample size than the CPS and data are independent from one year to the next.[a] A ten-year average has a smoothing effect on estimates, which diminishes economy-wide shocks to the productivity growth rate caused by cyclical and anomalous expansions and contractions of the economy. Incorporating data from the most recent decade produces estimates consistent with recent social, demographic, and economic trends affecting earnings, workforce participation, and educational attainment.
Life tables	Incorporates projected cohort life tables published by the SSA in the *Life tables underlying the SSA Trustees' 2015 annual report* ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Social Security Administration (SSA)</Author><Year>2015</Year><RecNum>219</RecNum><Prefix>SSA </Prefix><DisplayText>SSA 2015</DisplayText><record><rec-number>219</rec-number><foreign-keys><key app="EN" db-id="0a0wva05uf5wdvep9eex2dz052etaa2zdsxs" timestamp="1484253829">219</key></foreign-keys><ref-type name="Dataset">59</ref-type><contributors><authors><author>Social Security Administration (SSA),,</author></authors></contributors><titles><title>Life tables underlying the SSA Trustees' 2015 annual report, in Excel format.</title></titles><dates><year>2015</year></dates><publisher>Value Economics LLC</publisher><urls><related-urls><url>http://www.valueeconomics.com/data.html</url></related-urls></urls></record></Cite></EndNote>]) in place of those produced by the Centers for Disease Control and Prevention (CDC). While the CDC life tables reflect current cohorts, the SSA projected cohort life tables reflect mortality rates of a single cohort yet to be born. Male-female ratios for each age in the age profile (age 16 to age 80) are simulated from the SSA cohort life tables.
IQ-effect	Uses an updated Salkever IQ effect that was estimated using more recent 1997 National Longitudinal Survey of Youth (NLSY) data; these updated IQ effects are 1.865 percent for males and 3.397 percent for females. The justification for this is presented in Section B.1.
Educational attainment	Models postsecondary educational attainment for the target cohort using enrollment statistics and degrees conferred. Previous estimates account for declining educational attainment observed in older cohorts by assuming that educational attainment cannot decline.
Lost earnings and education costs	Estimates lost earnings while in school by taking the difference of average earnings for individuals enrolled in school and individuals not enrolled in school. Lost earnings are weighted by simulated levels of educational attainment. Previously, this has been estimated by assuming that individuals enrolled in school work part-time and individuals not enrolled in school work full-time.
	Weights education costs by school enrollment at each age rather than taking a straight average
	Weights education costs and lost earnings by the probability that an individual will attain additional education at a particular age rather than assuming that they accrue at the marginal education age
Discounting	Discounts lifetime earnings to a baseline age of 3 rather than 0

a. The CPS Annual Social and Economic Supplement (ASEC) has a longitudinal component resulting in some overlap of individuals sampled from one year to the next.

B.1 IQ Effect on Lifetime Earnings

For this analysis, the value of an IQ point as a percentage of lifetime earnings is taken from an EPA reanalysis of Salkever ([ADDIN EN.CITE ADDIN EN.CITE.DATA]), which follows the same approach as the original analysis but used more recent 1997 NLSY data instead of the original 1979 NLSY data. This EPA analysis indicates that a one point change in IQ results in a 1.865 percent and 3.397 percent change in lifetime earnings for males and females, respectively. The estimates incorporate the direct and indirect effects that changes in IQ have on earnings. Direct effects include the effect of IQ test scores on participation in employment and earnings with the years of schooling held constant. Indirect effects include the effect of IQ test scores on years of schooling attained, and the subsequent effect on participation and earnings.

Salkever ([ADDIN EN.CITE ADDIN EN.CITE.DATA]) also produces adjusted estimates that incorporate non-IQ related effects caused by lead exposure on schooling from Schwartz ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Schwartz</Author><Year>1994</Year><RecNum>621</RecNum><DisplayText>1994</DisplayText><record><rec-number>621</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357832">621</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Joel Schwartz</author></authors></contributors><auth-address>Department of Social and Preventive Medicine, University of Basal, Switzerland.</auth-address><titles><title>Societal benefits of reducing lead exposure</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>105-124</pages><volume>66</volume><number>1</number><keywords><keyword>Environmental Exposure/*economics</keyword><keyword>Environmental Exposure/*prevention & control</keyword><keyword>Lead/*adverse effects</keyword><keyword>Adult</keyword><keyword>Cardiovascular Diseases/chemically induced</keyword><keyword>Cardiovascular Diseases/prevention & control</keyword><keyword>Child</keyword><keyword>Cognition Disorders/chemically induced</keyword><keyword>Cognition Disorders/prevention & control</keyword><keyword>Cost-Benefit Analysis</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Lead/blood</keyword><keyword>Pregnancy</keyword><keyword>Prenatal Exposure Delayed Effects</keyword></keywords><dates><year>1994</year></dates><pub-location>UNITED STATES</pub-location><publisher>Academic Press</publisher><isbn>0013-9351</isbn><accession-num>8013434</accession-num><urls><related-urls><url>http://search.ebscohost.com/login.aspx?direct=true&db=mnh&AN=8013434&site=ehost-live</url></related-urls></urls><remote-database-name>mnh</remote-database-name><remote-database-provider>EBSCOhost</remote-database-provider></record></Cite></EndNote>]), yielding a 2.094 percent and 3.631 percent change in lifetime earnings for males and females, respectively. Non-IQ effects on schooling caused by lead exposure include effects on hearing, balance, hyperactivity, and perceptual and attention disorders ([ADDIN EN.CITE <EndNote><Cite><Author>Schwartz</Author><Year>1994</Year><RecNum>621</RecNum><DisplayText>Schwartz 1994</DisplayText><record><rec-number>621</rec-

number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357832">621</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Joel Schwartz</author></authors></contributors><auth-address>Department of Social and Preventive Medicine, University of Basal, Switzerland.</auth-address><titles><title>Societal benefits of reducing lead exposure</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>105-124</pages><volume>66</volume><number>1</number><keywords><keyword>Environmental Exposure/*economics</keyword><keyword>Environmental Exposure/*prevention & control</keyword><keyword>Lead/*adverse effects</keyword><keyword>Adult</keyword><keyword>Cardiovascular Diseases/chemically induced</keyword><keyword>Cardiovascular Diseases/prevention & control</keyword><keyword>Child</keyword><keyword>Cognition Disorders/chemically induced</keyword><keyword>Cognition Disorders/prevention & control</keyword><keyword>Cost-Benefit Analysis</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Lead/blood</keyword><keyword>Pregnancy</keyword><keyword>Prenatal Exposure Delayed Effects</keyword></keywords><dates><year>1994</year></dates><pub-location>UNITED STATES</pub-location><publisher>Academic Press</publisher><isbn>0013-9351</isbn><accession-num>8013434</accession-num><urls><related-urls><url>http://search.ebscohost.com/login.aspx?direct=true&db=mnh&AN=8013434&site=ehost-live</url></related-urls></urls><remote-database-name>mnh</remote-database-name><remote-database-provider>EBSCOhost</remote-database-provider></record></Cite></EndNote>]). Schwartz ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Schwartz</Author><Year>1994</Year><RecNum>621</RecNum><DisplayText>1994</DisplayText><record><rec-number>621</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357832">621</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Joel Schwartz</author></authors></contributors><auth-address>Department of Social and Preventive Medicine, University of Basal, Switzerland.</auth-address><titles><title>Societal benefits of reducing lead exposure</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>105-124</pages><volume>66</volume><number>1</number><keywords><keyword>Environmental Exposure/*economics</keyword><keyword>Environmental Exposure/*prevention & control</keyword><keyword>Lead/*adverse effects</keyword><keyword>Adult</keyword><keyword>Cardiovascular Diseases/chemically induced</keyword><keyword>Cardiovascular Diseases/prevention & control</keyword><keyword>Child</keyword><keyword>Cognition Disorders/chemically induced</keyword><keyword>Cognition Disorders/prevention & control</keyword><keyword>Cost-Benefit Analysis</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Lead/blood</keyword><keyword>Pregnancy</keyword><keyword>Prenatal Exposure Delayed Effects</keyword></keywords><dates><year>1994</year></dates><pub-location>UNITED

STATES</pub-location><publisher>Academic Press</publisher><isbn>0013-9351</isbn><accession-num>8013434</accession-num><urls><related-urls><url>http://search.ebscohost.com/login.aspx?direct=true&db=mnh&AN=8013434&site=ehost-live</url></related-urls></urls><remote-database-name>mnh</remote-database-name><remote-database-provider>EBSCOhost</remote-database-provider></record></Cite></EndNote>]) estimates lead exposure on schooling to be 0.131 years per IQ point,[12] whereas Salkever ([ADDIN EN.CITE ADDIN EN.CITE.DATA]) estimates the effect to be 0.1007 years per IQ point- the former estimate unsurprisingly larger given that it captures IQ and non-IQ effects of lead exposure.

In his meta-analysis, Salkever ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Salkever</Author><Year>2014</Year><RecNum>618</RecNum><DisplayText>2014</DisplayText><record><rec-number>618</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357687">618</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>David S. Salkever</author></authors></contributors><titles><title>Assessing the IQ-earnings link in environmental lead impacts on children: Have hazard effects been overstated?</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>219-230</pages><volume>131</volume><number>0</number><dates><year>2014</year></dates><isbn>0013-9351</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0013935114000644</url></related-urls></urls><electronic-resource-num>http://dx.doi.org/10.1016/j.envres.2014.03.018</electronic-resource-num></record></Cite></EndNote>]) only defended his unadjusted results, implying that Salkever believes his unadjusted results to be the most defensible. For this reason, Salkever's ([ADDIN EN.CITE ADDIN EN.CITE.DATA]) adjusted estimates incorporating Schwartz's ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Schwartz</Author><Year>1994</Year><RecNum>621</RecNum><DisplayText>1994</DisplayText><record><rec-number>621</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357832">621</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Joel Schwartz</author></authors></contributors><auth-address>Department of Social and Preventive Medicine, University of Basal, Switzerland.</auth-address><titles><title>Societal benefits of reducing lead exposure</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>105-124</pages><volume>66</volume><number>1</number><keywords><keyword>Environmental Exposure/*economics</keyword><keyword>Environmental Exposure/*prevention & control</keyword><keyword>Lead/*adverse effects</keyword><keyword>Adult</keyword><keyword>Cardiovascular Diseases/chemically

[12] Exposure sufficient to cause a one point decrement in IQ.

induced</keyword><keyword>Cardiovascular Diseases/prevention & control</keyword><keyword>Child</keyword><keyword>Cognition Disorders/chemically induced</keyword><keyword>Cognition Disorders/prevention & control</keyword><keyword>Cost-Benefit Analysis</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Lead/blood</keyword><keyword>Pregnancy</keyword><keyword>Prenatal Exposure Delayed Effects</keyword></keywords><dates><year>1994</year></dates><pub-location>UNITED STATES</pub-location><publisher>Academic Press</publisher><isbn>0013-9351</isbn><accession-num>8013434</accession-num><urls><related-urls><url>http://search.ebscohost.com/login.aspx?direct=true&db=mnh&AN=8013434&site=ehost-live</url></related-urls></urls><remote-database-name>mnh</remote-database-name><remote-database-provider>EBSCOhost</remote-database-provider></record></Cite></EndNote>]) effect on schooling were not updated and are not used to measure the effect of lead exposure on earnings in this analysis, despite the fact that omitting non-IQ effects on schooling may underestimate the actual IQ point dollar value associated with reducing lead exposure.

Because non-IQ effects on schooling are omitted, results presented here may be applied more generally to evaluate IQ decrements resulting from other toxins as well (e.g., mercury). However, if non-IQ effects on schooling are expected to be significant, the estimated benefits of preventing IQ decrements could be overly conservative.

B.2 Critical Review of Salkever's Estimates

Salkever's estimates of the impacts of IQ decrements on future earnings are greater than those of other authors, which has led to claims that they overstate the true impacts. Most notably, Grosse ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Grosse</Author><Year>2007</Year><RecNum>616</RecNum><DisplayText>2007</DisplayText><record><rec-number>616</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357601">616</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Scott D. Grosse</author></authors></contributors><titles><title>How Much Does IQ Raise Earnings? Implications for Regulatory Impact Analyses</title><secondary-title>Assoc. Environ. Resour. Econ. Newslett.</secondary-title></titles><periodical><full-title>Assoc. Environ. Resour. Econ. Newslett.</full-title></periodical><pages>17-20</pages><volume>27</volume><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>]) and Robinson ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Robinson</Author><Year>2013</Year><RecNum>619</RecNum><DisplayText>2013</DisplayText><record><rec-number>619</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357727">619</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Lisa A. Robinson</author></authors></contributors><titles><title>Lead: Regulations</title><secondary-title>Encyclopedia of Environmental Management</secondary-title></titles><pages>1636-1646</pages><volume>null</volume><number>null</number><num-vols>0</num-vols><dates><year>2013</year></dates><publisher>Taylor &

Francis</publisher><isbn>1-4398-2927-6</isbn><work-type>doi:10.1081/E-EEM-120047321</work-type><urls><related-urls><url>http://dx.doi.org/10.1081/E-EEM-120047321</url></related-urls></urls><electronic-resource-num>doi:10.1081/E-EEM-120047321</electronic-resource-num><access-date>2014/11/12</access-date></record></Cite></EndNote>]) present critical reviews of Salkever's estimates. Their concerns fall into two categories:

1. Measurement and statistical issues, and
2. Comparability of earnings impact results with recent findings in the labor economics literature.

Salkever ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Salkever</Author><Year>2014</Year><RecNum>618</RecNum><DisplayText>2014</DisplayText><record><rec-number>618</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357687">618</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>David S. Salkever</author></authors></contributors><titles><title>Assessing the IQ-earnings link in environmental lead impacts on children: Have hazard effects been overstated?</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>219-230</pages><volume>131</volume><number>0</number><dates><year>2014</year></dates><isbn>0013-9351</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0013935114000644</url></related-urls></urls><electronic-resource-num>http://dx.doi.org/10.1016/j.envres.2014.03.018</electronic-resource-num></record></Cite></EndNote>]) addresses the concerns of Grosse ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Grosse</Author><Year>2007</Year><RecNum>616</RecNum><DisplayText>2007</DisplayText><record><rec-number>616</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357601">616</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Scott D. Grosse</author></authors></contributors><titles><title>How Much Does IQ Raise Earnings? Implications for Regulatory Impact Analyses</title><secondary-title>Assoc. Environ. Resour. Econ. Newslett.</secondary-title></titles><periodical><full-title>Assoc. Environ. Resour. Econ. Newslett.</full-title></periodical><pages>17-20</pages><volume>27</volume><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>]) and Robinson ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Robinson</Author><Year>2013</Year><RecNum>619</RecNum><DisplayText>2013</DisplayText><record><rec-number>619</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357727">619</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Lisa A. Robinson</author></authors></contributors><titles><title>Lead: Regulations</title><secondary-title>Encyclopedia of Environmental Management</secondary-

title></titles><pages>1636-1646</pages><volume>null</volume><number>null</number><num-vols>0</num-vols><dates><year>2013</year></dates><publisher>Taylor & Francis</publisher><isbn>1-4398-2927-6</isbn><work-type>doi:10.1081/E-EEM-120047321</work-type><urls><related-urls><url>http://dx.doi.org/10.1081/E-EEM-120047321</url></related-urls></urls><electronic-resource-num>doi:10.1081/E-EEM-120047321</electronic-resource-num><access-date>2014/11/12</access-date></record></Cite></EndNote>]) by providing a meta-analysis of related studies. Salkever ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Salkever</Author><Year>2014</Year><RecNum>618</RecNum><DisplayText>2014</DisplayText><record><rec-number>618</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357687">618</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>David S. Salkever</author></authors></contributors><titles><title>Assessing the IQ-earnings link in environmental lead impacts on children: Have hazard effects been overstated?</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>219-230</pages><volume>131</volume><number>0</number><dates><year>2014</year></dates><isbn>0013-9351</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0013935114000644</url></related-urls></urls><electronic-resource-num>http://dx.doi.org/10.1016/j.envres.2014.03.018</electronic-resource-num></record></Cite></EndNote>]) provides convincing evidence in support of his original estimates. For example, the author found that many of the studies only included males and/or considered hourly wages instead of annual earnings with a participation effect. Because impacts are lower for males ([ADDIN EN.CITE <EndNote><Cite><Author>Salkever</Author><Year>2014</Year><RecNum>618</RecNum><DisplayText>Salkever 2014</DisplayText><record><rec-number>618</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357687">618</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>David S. Salkever</author></authors></contributors><titles><title>Assessing the IQ-earnings link in environmental lead impacts on children: Have hazard effects been overstated?</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>219-230</pages><volume>131</volume><number>0</number><dates><year>2014</year></dates><isbn>0013-9351</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0013935114000644</url></related-urls></urls><electronic-resource-num>http://dx.doi.org/10.1016/j.envres.2014.03.018</electronic-resource-num></record></Cite></EndNote>]), Salkever indicates that results from studies that only consider the impact of IQ decrements on male wages will be biased downward. In reference to the latter observation, Salkever ([ADDIN EN.CITE <EndNote><Cite

ExcludeAuth="1"><Author>Salkever</Author><Year>2014</Year><RecNum>618</RecNum><DisplayText>2014</DisplayText><record><rec-number>618</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357687">618</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>David S. Salkever</author></authors></contributors><titles><title>Assessing the IQ-earnings link in environmental lead impacts on children: Have hazard effects been overstated?</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>219-230</pages><volume>131</volume><number>0</number><dates><year>2014</year></dates><isbn>0013-9351</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0013935114000644</url></related-urls></urls><electronic-resource-num>http://dx.doi.org/10.1016/j.envres.2014.03.018</electronic-resource-num></record></Cite></EndNote>]) concludes that studies examining impacts on hourly wages omit the impact that IQ decrements have on workforce participation, again biasing the results downward. In fact, Salkever ([ADDIN EN.CITE ADDIN EN.CITE.DATA]) is the only analysis that separately estimates the IQ effect derived from average annual earnings and the participation effect for both males and females. For a full discussion of Salkever's response to critical review articles see Salkever ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Salkever</Author><Year>2014</Year><RecNum>618</RecNum><DisplayText>2014</DisplayText><record><rec-number>618</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357687">618</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>David S. Salkever</author></authors></contributors><titles><title>Assessing the IQ-earnings link in environmental lead impacts on children: Have hazard effects been overstated?</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>219-230</pages><volume>131</volume><number>0</number><dates><year>2014</year></dates><isbn>0013-9351</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0013935114000644</url></related-urls></urls><electronic-resource-num>http://dx.doi.org/10.1016/j.envres.2014.03.018</electronic-resource-num></record></Cite></EndNote>]).

As of the date of this report, the estimates published in Salkever ([ADDIN EN.CITE ADDIN EN.CITE.DATA]) remain the most appropriate for this analysis. Though the procedures and assumptions on which many of the related studies depend may be sound in themselves, they do not improve upon Salkever ([ADDIN EN.CITE ADDIN EN.CITE.DATA]), at least insomuch as the present analysis is concerned.

B.3 Method for Estimating Lifetime Earnings Stream

This section describes the methods used to estimate the average present value of the earnings stream of the affected birth cohort from age 16 to age 80. The universe of individuals from which

annual earnings and enrollment are estimated includes the civilian population only, excluding individuals living in institutional and non-institutional group quarters and unpaid workers.[13] Estimates are presented in 2017 dollars and are discounted using both a rate of 3 percent and of 7 percent.

Section [REF _Ref402355789 \r \h * MERGEFORMAT] describes the method used to estimate the distribution of educational attainment associated with each age in the age profile. Section [REF _Ref402355963 \r \h * MERGEFORMAT] describes the method used to estimate the annual earnings associated with each level of educational attainment for each age in the age profile. Section [REF _Ref402356068 \r \h * MERGEFORMAT] describes the life tables used in the lifetime earnings estimation and the derivation of male-female population ratios from the life tables. Section [REF _Ref402356221 \r \h * MERGEFORMAT] summarizes the lifetime earnings estimates. Section [REF _Ref402358029 \n \h * MERGEFORMAT] describes the effect changes in IQ have on lifetime earnings. Section [REF _Ref480970863 \n \h] presents a discussion of the limitations of this method.

B.3.1 Educational Attainment

Two methods are used to estimate the distribution of educational attainment over the age profile of the target birth cohort. One method is used to estimate primary and secondary school attainment, with the exception of grade 12, and a second method is used to estimate postsecondary school attainment. Section [REF _Ref403393937 \n \h] describes primary and secondary school attainment, and Section [REF _Ref402181341 \n \h] describes postsecondary school attainment.

B.3.1.1 Primary and Secondary School Attainment

Primary and secondary school attainment is estimated for ages 1 to 19 by estimating the average proportion of the population that has completed grades 1 to 11 for each age. Primary and secondary school attainment is estimated for ages 20 and older by estimating the average proportion of 20 to 25 year olds that have completed grades 1 to 11. ACS single-year PUMS from 2008 to 2017 are used to produce ten-year average primary and secondary school attainment estimates ([ADDIN EN.CITE <EndNote><Cite><Author>U.S. Census Bureau</Author><Year>2017</Year><RecNum>236</RecNum><DisplayText>U.S. Census Bureau 2017c</DisplayText><record><rec-number>236</rec-number><foreign-keys><key app="EN" db-id="9e2tazdvmef5axewx2ovx2xd92psp9ft9ets"

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[13] According to the Census Bureau, people not living housing units (e.g., house, apartment, mobile home, rented room) are classified as living in group quarters. As of 2006, the ACS sample includes both institutional group quarters (e.g., correctional facilities, nursing homes, and mental hospitals) and non-institutional group quarters (e.g., college dormitories, military barracks, group homes, missions, and shelters; [ADDIN EN.CITE <EndNote><Cite><Author>U.S. Census Bureau</Author><Year>2016</Year><RecNum>627</RecNum><DisplayText>U.S. Census Bureau 2016a</DisplayText><record><rec-number>627</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529590079">627</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>U.S. Census Bureau,</author></authors></contributors><titles><title>Group Quarters/Residence Rules</title></titles><volume>2017</volume><number>May 12</number><dates><year>2016</year><pub-dates><date>Apr. 13</date></pub-dates></dates><urls><related-urls><url>https://www.census.gov/topics/income-poverty/poverty/guidance/group-quarters.html</url></related-urls></urls></record></Cite></EndNote>]).

timestamp="1476715332">236</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S. Census Bureau,,</author></authors></contributors><titles><title>American Community Survey Single-year Public Use Microdata Sample</title></titles><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]).

B.3.1.2 Postsecondary School Attainment

Postsecondary educational attainment is estimated first by determining the age-sex distribution of degrees conferred and then by applying this distribution to the total number of degrees conferred. The age-sex distribution of enrollment in college and graduate school is used as a proxy for the age-sex distribution of degrees conferred. Lag times are used to stagger enrollment because of the length of time it takes to earn a degree. A lag time of one year is assigned to Associate's and Master's degrees, two years to Bachelor's degrees, and three years to doctoral degrees. For example, if 20 percent of males enrolled as undergraduates in college are 20 years old then it is assumed that 20 percent of Bachelor's degrees are awarded to 22 year old males.

The proportion of an age group receiving a degree is then calculated by dividing the number of degrees awarded at a particular age by the total number of people of the same age. To account for individuals receiving successive degrees from postsecondary institutions the proportion of individuals with a Bachelor's degree that previously received an Associate's degree (21 percent) is subtracted from the proportion of individuals with an Associate's degree[14] ([ADDIN EN.CITE <EndNote><Cite><Author>U.S. Department of Education</Author><Year>2009</Year><RecNum>630</RecNum><DisplayText>U.S. Department of Education 2009</DisplayText><record><rec-number>630</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529590244">630</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. Department of Education,, National Center for Education Statistics (NCES)</author></authors></contributors><titles><title>2003-04 Beginning Postsecondary Students Longitudinal Study, Second Follow-up (Computation by NCES PowerStats Version 1.0 on 11/3/2014)</title></titles><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]); the proportion of individuals receiving a Master's degree or receiving a doctoral degree without previously receiving a Master's degree (25 percent; [ADDIN EN.CITE <EndNote><Cite><Author>U.S. Department of Education</Author><Year>2003</Year><RecNum>629</RecNum><DisplayText>U.S. Department of Education 2003</DisplayText><record><rec-number>629</rec-

[14] Estimate based on the 2003-04 Beginning Postsecondary Students Longitudinal Study ([ADDIN EN.CITE <EndNote><Cite><Author>U.S. Department of Education</Author><Year>2009</Year><RecNum>630</RecNum><DisplayText>U.S. Department of Education 2009</DisplayText><record><rec-number>630</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529590244">630</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. Department of Education,, National Center for Education Statistics (NCES)</author></authors></contributors><titles><title>2003-04 Beginning Postsecondary Students Longitudinal Study, Second Follow-up (Computation by NCES PowerStats Version 1.0 on 11/3/2014)</title></titles><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]).

number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529590240">629</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. Department of Education,, National Center for Education Statistics (NCES)</author></authors></contributors><titles><title>Baccalaureate and Beyond Longitudinal Study 1993-2003 (Computation by NCES PowerStats Version 1.0 on 11/6/2014)</title></titles><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>]) is subtracted from the proportion of individuals receiving a Bachelor's degree; and the proportion of individuals receiving a doctoral degree that previously received a Master's degree is subtracted from the proportion of individuals with a Master's degree (75 percent; [ADDIN EN.CITE <EndNote><Cite><Author>U.S. Department of Education</Author><Year>2003</Year><RecNum>629</RecNum><DisplayText>U.S. Department of Education 2003</DisplayText><record><rec-number>629</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529590240">629</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. Department of Education,, National Center for Education Statistics (NCES)</author></authors></contributors><titles><title>Baccalaureate and Beyond Longitudinal Study 1993-2003 (Computation by NCES PowerStats Version 1.0 on 11/6/2014)</title></titles><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>]).[15, 16] The cumulative proportion of degrees conferred at a particular age represents the proportion of the population for whom the corresponding degree is the highest level of education attained.

Enrollment statistics are estimated from 2008 to 2017 using ACS single-year PUMS. Data describing Associate's, Bachelor's, Master's, and doctoral degrees conferred are taken from the 2016 Digest of Education Statistics, published by the National Center for Education Statistics (NCES) ([ADDIN EN.CITE <EndNote><Cite><Author>Snyder</Author><Year>2016</Year><RecNum>623</RecNum><DisplayText>Snyder & Dillow 2016</DisplayText><record><rec-number>623</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529359494">623</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Thomas D. Snyder</author><author>Sally A. Dillow</author></authors></contributors><titles><title>Digest of Education Statistics 2015</title></titles><dates><year>2016</year></dates><pub-location>Washington, DC</pub-location><publisher>National Center for Education Statistics, Institute of Education Sciences,

[15] Estimate based on the 1993 Baccalaureate and Beyond Longitudinal Study ([ADDIN EN.CITE <EndNote><Cite><Author>U.S. Department of Education</Author><Year>2003</Year><RecNum>629</RecNum><DisplayText>U.S. Department of Education 2003</DisplayText><record><rec-number>629</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529590240">629</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>U.S. Department of Education,, National Center for Education Statistics (NCES)</author></authors></contributors><titles><title>Baccalaureate and Beyond Longitudinal Study 1993-2003 (Computation by NCES PowerStats Version 1.0 on 11/6/2014)</title></titles><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>]). The actual figure is 74.3.

[16] Educational attainment does not account for individuals receiving a second degree within the same attainment group later in life. For example, a second Master's degree is treated as two individuals with a Master's degree.

U.S. Department of Education</publisher><urls><related-urls><url>https://nces.ed.gov/programs/digest/2016menu_tables.asp</url></related-urls></urls><access-date>Oct. 06, 2016</access-date></record></Cite></EndNote>]). Data describing degrees conferred in the years 2016 and 2017 are projected by the NCES.

B.3.2 Average Annual Earnings

Annual earnings for males and females are estimated from ACS single-year PUMS for each of the levels of educational attainment previously described for ages ranging from 16 to 80, for each year from 2008 to 2017. Average annual earnings for males and females are equal to the sum of annual earnings associated with each level of educational attainment weighted by the distribution of educational attainment for each year in the age profile of the target birth cohort. Earnings consist of pre-tax wages and salary.

B.3.2.1 Topcodes

For confidentiality reasons, the Census Bureau topcodes reported income components if it falls below or above a predetermined threshold before making the data publicly available. Amounts above or below the threshold are replaced with the state mean value above or below the threshold ([ADDIN EN.CITE <EndNote><Cite><Author>U.S. Census Bureau</Author><Year>2013</Year><RecNum>626</RecNum><DisplayText>U.S. Census Bureau 2013</DisplayText><record><rec-number>626</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529589874">626</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>U.S. Census Bureau,</author></authors></contributors><titles><title>Public Use Microdata Sample (PUMS) Files: 2013 PUMS Top Coded and Bottom Coded Values</title></titles><dates><year>2013</year></dates><urls><related-urls><url>http://www.census.gov/acs/www/Downloads/data_documentation/pums/TopCodedValues/2013PUMS_top_coded_values.pdf</url></related-urls></urls></record></Cite></EndNote>]).

B.3.2.2 Real Earnings Growth Rate

Real earnings fluctuate from one year to the next in response to trends in the inflation rate and the economy-wide productivity growth rate ([ADDIN EN.CITE <EndNote><Cite><Author>Thornton</Author><Year>1997</Year><RecNum>622</RecNum><DisplayText>Thornton et al. 1997</DisplayText><record><rec-number>622</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529358532">622</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Thornton, Robert J.</author><author>Rogers, James D.</author><author>Brookshire, Michael L.</author></authors></contributors><titles><title>On the Interpretations of Age-Earnings Profiles</title><secondary-title>Journal of Labor Research</secondary-title></titles><periodical><full-title>Journal of Labor Research</full-title></periodical><pages>351-365</pages><volume>18</volume><number>2</number><keywords><keyword>WAGES</keyword><keyword>UNITED States</keyword></keywords><dates><year>1997</year><pub-dates><date>Spring97</date></pub-dates></dates><publisher>Springer Science &

Business Media B.V.</publisher><isbn>01953613</isbn><accession-num>9703123451</accession-num><work-type>Article</work-type><urls><related-urls><url>http://search.ebscohost.com/login.aspx?direct=true&db=plh&AN=9703123451&site=ehost-live</url></related-urls></urls><remote-database-name>plh</remote-database-name><remote-database-provider>EBSCOhost</remote-database-provider></record></Cite></EndNote>]). An annual growth rate of 1 percent is incorporated into the annual earnings estimates. Grosse et al. ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Grosse</Author><Year>2002</Year><RecNum>617</RecNum><DisplayText>2002</DisplayText><record><rec-number>617</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357617">617</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Scott D. Grosse</author><author>Thomas D. Matte</author><author>Joel Schwartz</author><author>Richard J. Jack</author></authors></contributors><titles><title>Economic Gains Resulting from the Reduction in Children's Exposure to Lead in the United States</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>563</pages><volume>110</volume><number>6</number><keywords><keyword>INDUSTRIAL productivity</keyword><keyword>LEAD -- Environmental aspects</keyword><keyword>UNITED States</keyword></keywords><dates><year>2002</year></dates><publisher>Superintendent of Documents</publisher><isbn>00916765</isbn><accession-num>6879146</accession-num><work-type>Article</work-type><urls><related-urls><url>https://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=6879146&site=eds-live</url></related-urls></urls><remote-database-name>a9h</remote-database-name><remote-database-provider>EBSCOhost</remote-database-provider></record></Cite></EndNote>]) and Schwartz ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Schwartz</Author><Year>1994</Year><RecNum>621</RecNum><DisplayText>1994</DisplayText><record><rec-number>621</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357832">621</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Joel Schwartz</author></authors></contributors><auth-address>Department of Social and Preventive Medicine, University of Basal, Switzerland.</auth-address><titles><title>Societal benefits of reducing lead exposure</title><secondary-title>Environmental Research</secondary-title></titles><periodical><full-title>Environmental research</full-title></periodical><pages>105-124</pages><volume>66</volume><number>1</number><keywords><keyword>Environmental Exposure/*economics</keyword><keyword>Environmental Exposure/*prevention & control</keyword><keyword>Lead/*adverse effects</keyword><keyword>Adult</keyword><keyword>Cardiovascular Diseases/chemically induced</keyword><keyword>Cardiovascular Diseases/prevention & control</keyword><keyword>Child</keyword><keyword>Cognition Disorders/chemically induced</keyword><keyword>Cognition Disorders/prevention & control</keyword><keyword>Cost-Benefit

Analysis</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Lead/blood</keyword><keyword>Pregnancy</keyword><keyword>Prenatal Exposure Delayed Effects</keyword></keywords><dates><year>1994</year></dates><pub-location>UNITED STATES</pub-location><publisher>Academic Press</publisher><isbn>0013-9351</isbn><accession-num>8013434</accession-num><urls><related-urls><url>http://search.ebscohost.com/login.aspx?direct=true&db=mnh&AN=8013434&site=ehost-live</url></related-urls></urls><remote-database-name>mnh</remote-database-name><remote-database-provider>EBSCOhost</remote-database-provider></record></Cite></EndNote>]) calculate lifetime earnings using a 1 percent growth rate in similar analyses. This rate is also consistent with long term historical averages; for example, the average percent change in real annual earnings from the year 1967 to 2016 as derived from Historical Income Tables published by the U.S. Census Bureau ([ADDIN EN.CITE <EndNote><Cite><Author>U.S. Census Bureau</Author><Year>2017</Year><RecNum>628</RecNum><DisplayText>U.S. Census Bureau 2017d</DisplayText><record><rec-number>628</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529590176">628</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>U.S. Census Bureau,,</author></authors></contributors><titles><title>Historical Income Tables: People</title><secondary-title>Table P-42. Work Experience--All Workers by Mean Earnings and Sex: 1967 to 2016</secondary-title></titles><pages>Current Population Survey, Annual Social and Economic Supplements</pages><volume>2018</volume><number>Jan. 19</number><dates><year>2017</year><pub-dates><date>Aug. 10, 2017</date></pub-dates></dates><urls><related-urls><url>https://www2.census.gov/programs-surveys/cps/tables/time-series/historical-income-people/p42ar.xls</url></related-urls></urls></record></Cite></EndNote>]).

B.3.3 Life Tables and Male-female Ratios

B.3.3.1 Life Tables

Life tables present the survival rate or the probability that an individual will survive from age N to age N+1 (e.g. a 60 year old living to 61). Because some individuals die before retirement, the survival rate represents the probability of receiving earnings each year. As an individual ages, the probability declines. Future birth cohorts are expected to live longer, increasing the probability of living to age N+1, thereby increasing the average lifetime earnings for the cohort.

This analysis relies on the *Life tables underlying the SSA Trustees' 2015 annual report*, which are published on the website of Value Economics LLC ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Social Security Administration (SSA)</Author><Year>2015</Year><RecNum>243</RecNum><Prefix>SSA </Prefix><DisplayText>SSA 2015</DisplayText><record><rec-number>243</rec-number><foreign-keys><key app="EN" db-id="9e2tazdvmef5axewx2ovx2xd92psp9ft9ets" timestamp="1476715336">243</key></foreign-keys><ref-type name="Dataset">59</ref-type><contributors><authors><author>Social Security Administration (SSA),,</author></authors></contributors><titles><title>Life tables underlying the SSA Trustees' 2015 annual report, in Excel format.</title></titles><dates><year>2015</year></dates><publisher>Value Economics

LLC</publisher><urls><related-urls><url>http://www.valueeconomics.com/data.html</url></related-urls></urls></record></Cite></EndNote>]).[17] The SSA develops projected life tables for future birth cohorts. In this analysis, the life tables associated with the 2015 birth cohort are incorporated to represent a recent cohort.

B.3.3.2 Male-Female Ratios

Male-female ratios are needed to develop a weighted average of annual earnings. Historically, females have had higher survival rates than males which results in a female majority that increases as the population ages. Weighting earnings with male-female ratios allows average earnings to reflect the gender composition of the birth cohort at each age in the age profile.

Male-female ratios are forecasted by adjusting the male-female ratios present at age zero for each subsequent age using the survival rates from the life tables. The baseline male-female ratios are calculated from the *2014 National Population Projections* dataset, 2016 birth cohort ([ADDIN EN.CITE <EndNote><Cite><Author>U.S. Census Bureau</Author><RecNum>239</RecNum><DisplayText>U.S. Census Bureau 2014a</DisplayText><record><rec-number>239</rec-number><foreign-keys><key app="EN" db-id="9e2tazdvmef5axewx2ovx2xd92psp9ft9ets" timestamp="1476715335">239</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>U.S. Census Bureau,,</author></authors></contributors><titles><title>2014 National Population Projections</title></titles><volume>2017</volume><number>Jan. 10</number><dates><year>2014</year><pub-dates><date>Apr. 6, 2017</date></pub-dates></dates><urls><related-urls><url>https://www2.census.gov/programs-surveys/popproj/datasets/2014/2014-popproj/np2014_d1.csv</url></related-urls></urls></record></Cite></EndNote>]).

B.3.4 Present Value of Lifetime Earnings

Age-earnings profiles are estimated for the years 2008 through 2017. Average earnings are calculated for each year, Step 1, and then the ten averages are averaged to produce the grand mean earnings estimates presented in this report, Step 2:

Step 1

$$NPV_{yr} = \sum_{N=3}^{80} S_m \left(\frac{Y_{N,m} P_{N,m} R_{N,m} (1+X)^{N-A+0.5}}{((1+r)^{N-A+1})} \right) + S_f \left(\frac{Y_{N,f} P_{N,f} R_{N,f} (1+X)^{N-A+0.5}}{((1+r)^{N-A+1})} \right)$$

where:

NPV = the net present value of earnings between ages A and 80;
yr= survey year from 2008 to 2017
A = current age, which is 3 in this analysis;

[17] Value Economics LLC requested the life tables from the SSA. The SSA does not publish the tables on their website.

S = share of total population that is male or female;
N = ages in the future (3, ..., 80);
Y = average annual earnings among earners for a particular age (N);
P = survival rate for a particular age (N);
R = percent of population with earnings;
m = male indicator;
f = female indicator;
X = productivity rate assumed at the midpoint of age N; and
r = discount rate for the beginning of age N.

Step 2

$$NPV_{average} = \sum_{yr=2007}^{2016} \frac{(NPV_{yr})}{10}$$

where:

NPV = the net present value of earnings between ages A and 80; and
yr = survey year;

Lifetime earnings are discounted at both 3 percent and 7 percent, and the model assumes that real earnings will increase by 1 percent per year. Earnings are assumed to be zero for individuals under the age of 16 and over the age of 80. [REF _Ref532978217 \h] presents average lifetime earnings for males, females, and for the population from 2007 to 2016.

Exhibit [STYLEREF 5 \s]-[SEQ Table * ARABIC \s 5]: Lifetime Earnings (2017$)

Earnings Group	Discount Rate	
	3%	7%
Population	$884,342	$205,144
Male	$1,069,129	$244,738
Female	$695,243	$164,27

B.4 Effects on Earnings from Changes in IQ

The value of an IQ point is estimated by considering the direct and indirect effects of changes in IQ on earnings, as well as the costs associated with additional years of education. The cost of additional education is comprised of the direct cost of education and forgone earnings while in school.

Section [REF _Ref402356387 \r \h * MERGEFORMAT] describes the parameter used to estimate the total value of an IQ point, Section [REF _Ref402356468 \r \h] describes the methods used to estimate the components of costs associated with additional education, and Section [REF _Ref402356509 \r \h] presents the estimate for the net value of an IQ point.

B.4.1 Total Value of an IQ Point

The EPA's updated analysis based on Salkever ([ADDIN EN.CITE ADDIN EN.CITE.DATA]) yields a value of an IQ point equal to 1.865 percent and 3.397 percent of earnings for males and females, respectively. The average value of an IQ point is $23,269 and $5,398 discounted at a rate of 3 percent and 7 percent, respectively.

B.4.2 Additional Education: Costs and Lost Earnings

The effect of lead exposure on schooling is estimated to be 0.0811 years per IQ point for males and 0.0916 years per IQ point for females in the EPA's reanalysis of Salkever ([ADDIN EN.CITE ADDIN EN.CITE.DATA]). Increases in educational attainment signify analogous increases in education costs and diminished earnings resulting from working fewer hours while in school. To accurately portray the benefits of a population with a higher average IQ, the average value of an IQ point is adjusted to reflect the cost of additional education and the opportunity cost of being in school.

ACS PUMS data on enrollment were used to estimate both: (1) the ages at which the marginal increases in educational attainment due to higher IQ would be realized, and (2) the levels of additional educational attainment that would be achieved.

The distribution of ages at which the last year of education was obtained was estimated based on changes in the percentages of the population enrolled in school by age. For example, if 95 percent of 16 year olds are enrolled in school and 90 percent of 17 year olds are enrolled in school, it was estimated that 5 percent (95 percent minus 90 percent) of the population attained their last year of education at age 16. Thus, the analysis assumes that for 5 percent of the population, the marginal increase in educational attainment would be realized at age 17 – one year after they achieved their highest level of education in the baseline.

The level of additional education attained is estimated based on the enrollment for the ages at which the additional education is realized. For example, if 30 percent of enrolled 18 year olds are enrolled in 12th grade and 70 percent of enrolled 18 year olds are enrolled in university, the analysis estimates that additional education attained at age 18 is 30 percent 12th grade and 70 percent university.

B.4.2.1 Education Costs

Education costs associated with pursuing additional education are determined by the level of education being pursued. Three categories of education are considered in estimating costs:

- Public elementary and secondary schools (expenditures per pupil enrolled);
- Average undergraduate tuition (including fees, room, and board); and
- Average graduate tuition (including required fees).

Data describing the cost of education are taken from the 2016 version of the Digest of Education Statistics ([ADDIN EN.CITE <EndNote><Cite><Author>Snyder</Author><Year>2016</Year><RecNum>623</RecNum><DisplayText>Snyder & Dillow 2016</DisplayText><record><rec-number>623</rec-

number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529359494">623</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Thomas D. Snyder</author><author>Sally A. Dillow</author></authors></contributors><titles><title>Digest of Education Statistics 2015</title></titles><dates><year>2016</year></dates><pub-location>Washington, DC</pub-location><publisher>National Center for Education Statistics, Institute of Education Sciences, U.S. Department of Education</publisher><urls><related-urls><url>https://nces.ed.gov/programs/digest/2016menu_tables.asp</url></related-urls></urls><access-date>Oct. 06, 2016</access-date></record></Cite></EndNote>]).

For each age in the age profile an individual has a likelihood of pursuing additional education in one of the three categories listed above, and therefore of incurring corresponding education costs. Enrollment is used to determine each category's relative likelihood thereby allowing costs to be apportioned appropriately with respect to each age in the age profile. For example, at age 17, most individuals will be enrolled in secondary schools causing the cost of education to primarily reflect the costs associated with the first category of education.

The total cost of education for the target cohort is estimated by calculating the sum of education costs corresponding to each level of attainment, weighted by enrollment and the probability of pursuing additional education at age N. For example, suppose that 100 percent of the target cohort's females attain additional education at age 18 or age 19. Twenty-five percent of the target cohort females attain additional education at age 18 and 75 percent of the target cohort females attain additional education at age 19. At age 18, 30 percent of the target cohort currently enrolled in school is enrolled in 12th grade and 70 percent is enrolled in an undergraduate university. At age 19, 10 percent of the target cohort females currently enrolled in school are enrolled in 12th grade and 90 percent are enrolled in an undergraduate university. The annual cost of a secondary school and an undergraduate university is $12,000 and $20,000, respectively. As shown in [REF _Ref532978255 \h], the weighted cost of education per IQ point (assuming 0.0916 additional years of education) for the target cohort females is $1,722, $403 and $1,319 for 18 and 19 year olds, respectively.

Exhibit [STYLEREF 5 \s]-[SEQ Table * ARABIC \s 5]: Example of Education Cost Calculation

Age	Enrollment		Annual Cost of Ed.		Additional Ed. Weight	Weighted Costs	Cost per IQ Point
	12th Grade	University	12th Grade	University			
	a	*b*	*c*	*d*	*e*	*f=((a·c)+(b·d))·e*	f ·.0916
18	30%	70%	$12,000	$20,000	25%	$4,400	$403
19	10%	90%			75%	$14,400	$1,319
Total						**$18,800**	**$1,722**

B.4.2.2 Lost Earnings

Lost earnings are calculated by separately estimating annual earnings for individuals enrolled in school and not enrolled in school according to the method detailed in Section [REF _Ref402355963 \n \h], and taking the difference of the two estimates. The difference in earnings is assumed to be zero for a given age and sex combination if enrolled and/or not enrolled

earnings estimates rely on fewer than 150 observations. As with education costs, the differences in annual earnings are weighted by the probability that an individual will pursue additional education at their current age, N, as described at the beginning of this section. Lost earnings associated with an additional IQ point are generated by applying the EPA's IQ effect on schooling to the difference in annual earnings between the enrolled and not enrolled populations.

B.4.2.3 Summary of Additional Education Costs

The average estimated costs for additional education (tuition plus lost earnings) are $1,592 and $691, discounted at a rate of 3 percent and 7 percent, respectively.

B.4.3 Net Value of an IQ Point

The net value of an IQ point is equal to the total value minus the costs of attaining additional education. The estimates presented in [REF _Ref532978264 \h] are averages produced from ten years of ACS single-year PUMS covering the years 2008 through 2017.

Exhibit [STYLEREF 5 \s]-[SEQ Table * ARABIC \s 5]: Effects of a One Point Change in IQ on Earnings (2017$)

Estimate Parameter	Discount Rate	
	3%	7%
IQ value	$23,269	$5,398
Additional education costs and lost earnings	$1,592	$691
IQ value without education costs and lost earnings	$21,677	$4,707

B.5 Discussion of Methods

This section includes a discussion of the methods used to estimate the lifetime earnings stream.

B.5.1 Cross-Sectional Data

A single cross-section of data provides economic earnings data for individuals of different ages at one point in time. Thus, each age represented in a cross-section also represents a different birth cohort. Age-earnings profiles are often constructed with one cross-section of earnings data; however, there exists much controversy over this method. Even though this analysis averages the age-earnings profiles of 10 cross-sections of data, it is not a substitute for longitudinal data. The consensus is that age-earning profiles based on cross-sectional data underestimate earnings as individuals near retirement. If this is the case, lifetime earnings estimates based on cross-sectional data would be biased downward.

B.5.2 School Enrollment

The ACS PUMS do not have a variable indicating whether individuals are enrolled in school as full-time or part-time students. Because an additional year of educational attainment ostensibly refers to a student enrolled in school full-time for one academic school year, inclusion of part-time students may bias lost earnings estimates downwards, thereby resulting in a higher valuation of an IQ point. However, lost earnings estimates are based primarily on individuals enrolled in secondary school and undergraduate degree programs, where full-time enrollment is more common.

B.5.3 Labor Force Participation Rate

Average earnings are estimated as a function of average labor force participation rates from 2008 to 2017. The participation rates of some subpopulations will likely change over the course of the target cohort's lifespan, especially the female and elderly participation rates. Assuming the female and elderly participation rates continue to rise, estimates presented in this report would underestimate average lifetime earnings.

B.6 Limitations

B.6.1 Compensatory and Special Education

Compensatory education and special education costs are not reflected in the IQ point dollar value presented in this report. Compensatory education may be needed for individuals who experience high blood lead levels during infancy and special education may be needed for individuals with an IQ below 70. Reducing exposure to lead at an early age is expected to reduce the incidence of children requiring compensatory and/or special education, which would in turn lower associated costs. Though these costs are not anticipated to be a substantial component of the overall benefits, they do represent a potential benefit of reducing lead exposure.

B.6.2 Nonmarket Work

The use of earnings is an incomplete measure of an individual's value to society. This is particularly true for individuals who choose to not participate in the labor force for all of their working years. If the opportunity cost of non-wage compensated work is assumed to be the average wage earned by persons of the same sex, age, and education, the average lifetime earnings estimates for these people would be significantly higher.

B.6.3 Multiple Degrees

Individuals receiving a second degree within the same attainment group later in life are not taken into account. For example, a second Master's degree is treated as two individuals with a Master's degree. This would increase the proportion of individuals with degrees from postsecondary schooling institutions. Given that a minority of individuals would fall into this attainment category, the lifetime earnings estimate is not expected to be substantially impacted.

B.6.4 Earnings Growth Rate

The earnings growth rate for females is substantially higher than the rate for males. A portion of the difference is likely due to females approaching equal pay to males over time. However, a portion of the difference is likely an artifact of rising female labor force participation, hours worked per year, and educational attainment. These trends have tapered off overtime and in all likelihood will continue to do so. Therefore, the average growth rate of real wages for the 2017 birth cohort may be closer to the earnings growth rate for males compared to older cohorts.

B.6.5 Income vs. Earnings

Although earnings is a significant component of income for the middle quintiles of the distribution of income, Barth et al. ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Barth</Author><Year>1984</Year><RecNum>620</RecNum><DisplayText>1984</DisplayText><record><rec-number>620</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp"

timestamp="1529357814">620</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Barth, Michael C. </author><author>Janney III, Asa M.</author><author>Arnold, Frank</author><author>Sheiner, Louis</author></authors></contributors><titles><title>A Survey of the Literature Regarding the Relationship between Measures of IQ and Income</title><secondary-title>EPA Contract 68-01-6614</secondary-title></titles><dates><year>1984</year></dates><publisher>ICF, Washington, DC</publisher><urls></urls></record></Cite></EndNote>]) indicates that income may be substantially different from earnings for the tails of the income distribution. Therefore, earnings are assumed to be a good proxy for income in accordance with Salkever ([ADDIN EN.CITE ADDIN EN.CITE.DATA]).

B.6.6 Benefits

Because benefits have become a greater portion of income, their exclusion could result in lifetime earnings to be underestimated.

B.6.7 Impact of Ability on Earnings

Barth et al. ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Barth</Author><Year>1984</Year><RecNum>620</RecNum><DisplayText>1984</DisplayText><record><rec-number>620</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357814">620</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Barth, Michael C. </author><author>Janney III, Asa M.</author><author>Arnold, Frank</author><author>Sheiner, Louis</author></authors></contributors><titles><title>A Survey of the Literature Regarding the Relationship between Measures of IQ and Income</title><secondary-title>EPA Contract 68-01-6614</secondary-title></titles><dates><year>1984</year></dates><publisher>ICF, Washington, DC</publisher><urls></urls></record></Cite></EndNote>]) found that many studies concluded that the impact of ability on earnings increases with age. Therefore, estimates of the impact of IQ on earnings derived from younger individuals may be smaller than if estimates were derived from individuals over the age of 30 ([ADDIN EN.CITE <EndNote><Cite><Author>Barth</Author><Year>1984</Year><RecNum>620</RecNum><DisplayText>Barth et al. 1984</DisplayText><record><rec-number>620</rec-number><foreign-keys><key app="EN" db-id="astfddffk2fvdhe99z7p9wreavxffwde9dwp" timestamp="1529357814">620</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Barth, Michael C. </author><author>Janney III, Asa M.</author><author>Arnold, Frank</author><author>Sheiner, Louis</author></authors></contributors><titles><title>A Survey of the Literature Regarding the Relationship between Measures of IQ and Income</title><secondary-title>EPA Contract 68-01-6614</secondary-title></titles><dates><year>1984</year></dates><publisher>ICF, Washington, DC</publisher><urls></urls></record></Cite></EndNote>]). The EPA reanalysis of Salkever ([ADDIN EN.CITE ADDIN EN.CITE.DATA]) relies on data where respondents range in age from 27 to 32. Thus, the estimate of the impact of IQ on earnings may underestimate the true impact of ability on earnings.

Appendix C. Detailed Cost Calculations and Methods

This appendix provides detailed calculations for the cost analysis described in Section [REF _Ref525051776 \r \h]. Section [REF _Ref536441817 \r \h] provides detailed cost curves and the blending equation used to estimate control costs. Section [REF _Ref536441838 \r \h] describes the sources and methods used to estimate PWS wage rates. Section [REF _Ref536441856 \r \h] provides detailed calculations of the household-level control costs.

C.1 Capital and O&M Control Cost Details

To generate costs for the treatment technologies discussed in Section [REF _Ref523415174 \r \h], the EPA used its WBS cost-estimating models. The WBS models are spreadsheet-based engineering models for individual treatment technologies that are linked to a central database of component unit costs.

For each scenario modeled and separately for total capital and for O&M costs, the EPA fit up to three curves: one covering small systems (less than 1 MGD design flow), one covering medium systems (1 MGD to less than 10 MGD design flow), and one covering large systems (10 MGD design flow and greater). For each curve fit, the EPA selected from among several possible equation forms: linear, quadratic, cubic, power, exponential, and logarithmic. The EPA chose the form that resulted in the best correlation coefficient (R^2), subject to the requirement that the equation must be monotonically increasing over the appropriate range of flow rates (i.e., within the flow rate category, the equation must always result in higher estimated costs for higher flow systems than for lower flow systems).

For the selected technology (medium-cost perchlorate-selective 170,000 BV), the costs are calculated based on the following equation:

$$Cost = C7 \times Q^3 + C8 \times Q^2 + C9 \times Q + C10$$

where Q is treatment process design flow (MGD) for total capital costs or treatment process average flow (MGD) for annual O&M costs. [REF _Ref536441529 \h] shows the values for C7 through C10 for the selected technology based on the water source (groundwater or surface water) and system size.

Exhibit [STYLEREF 5 \s]-[SEQ Table * ARABIC \s 5]: Capital and O&M Control Cost Curve Parameters

Source	Size	Cost Type	C7	C8	C9	C10	Useful Life
GW	Small	O&M	56351.5	-50187.5	122627.1	4364.815	17.69411765
GW	Medium	O&M	0	0	133861.3	29816.62	31.74
GW	Large	O&M	0	0	122526.4	48879.59	33.95882353
SW	Small	O&M	0	-18636.8	118095.4	4401.098	17.69411765
SW	Medium	O&M	0	0	136673.8	28097.73	31.74
SW	Large	O&M	0	0	123719.9	66316.38	33.97058824
GW	Small	Total capital	111665.4	-213210	435508.3	125329.7	17.69411765
GW	Medium	Total capital	802.1603	-17543.4	455922.7	687296.4	31.74
GW	Large	Total capital	0	0	287995.3	1130876	33.95882353
SW	Small	Total capital	111750.5	-213364	435584.9	125332.8	17.69411765
SW	Medium	Total capital	830.5377	-17999.3	457555.7	685792.9	31.74

Source	Size	Cost Type	C7	C8	C9	C10	Useful Life
SW	Large	Total capital	0	0	287250.1	1144962	33.97058824

Additionally, given the high perchlorate removal efficiencies achieved by the treatment technology, the EPA assumes that systems can blend treated water and untreated water to meet the MCL. As such, the EPA applied the above equations using treatment process flows that account for the blending rate, which is the proportion of influent water that must be treated. For example, a blending rate of 0.6 means 60 percent of the water is treated and then blended with 40 percent untreated water. This rate depends on baseline perchlorate concentration, the treatment target concentration, and the removal efficiency of the treatment process (i.e., the percent of baseline perchlorate removed during treatment). For a treatment efficiency of 95 percent (or 0.95), the following equation defines the treatment target concentration of perchlorate (P_t) as a weighted average of the baseline concentration (P_b) and the treated water concentration [P_b x (1-0.95)] where the weights – based on the blending rate (B) – are (1-B) for the untreated water and B for the treated water:

$$P_t = (1 - B) \times P_b + B \times (P_b \times (1 - 0.95)).$$

Rearranging terms to solve for B (the blending rate) shows that the blending rate increases when the baseline concentration increases or the treatment target concentration decreases.

$$B = \frac{(P_b - P_t)}{P_b \times 0.95}$$

In turn, the equation presented above uses treatment process flow as the independent variable. Treatment process flow can be calculated from entry point flow by incorporating the blending rate as follows:

$$\text{Treatment Process Flow} = \text{B} \times \text{Entry Point Flow}$$

C.2 PWS Labor Rate Calculations

Section [REF _Ref536453331 \r \h] summarizes the PWS labor rate used to estimate the administrative and reporting burden. This section describes the calculation of the labor rate in more detail. First, the EPA identified the labor rates in the WBS models for technical staff (i.e., a full-time treatment plant operators) and managerial staff (i.e., utility managers for smaller systems and environmental managers for larger systems). Then, EPA calculated a weighted wage rate for each system size range based on these labor rates and assumed division of labor among technical and managerial staff. [REF _Ref536453391 \h] summarizes this calculation for each size range category; the weighted wage rate is calculated as follows:

$$Weighted = \sum_{i=1}^{7} CWS_i \, (R_{t,i} \times W_{t,i} + R_{m,i} \times W_{m,i}) \, / \, \sum_{i=1}^{7} CWS_i$$

Where:

Weighted = Overall system wage rate for labor associated with the proposed rule
R = hourly loaded wage rate
W = assigned weight for labor category
t = indicator for technical labor category
m = indicator for managerial labor category
s = indicator for size stratum
CWS = number of CWS by size stratum.

Exhibit [STYLEREF 5 \s]-[SEQ Table * ARABIC \s 5]: PWS Wage Rate Assumptions (2017$)

System Size (Population)	Technical Wage Rate[a]	Managerial Wage Rate[a]	Technical Weight	Managerial Weight	Weighted[b]	Number of Systems[c]
0-100	$31.91	$45.24	90%	10%	$33.24	10,838
101-500	$31.91	$45.24	90%	10%	$33.24	14,166
501-1,000	$31.91	$45.24	90%	10%	$33.24	5,117
1,001-3,300	$31.91	$45.24	90%	10%	$33.24	7,697
3,301-10,000	$34.05	$51.74	70%	30%	$39.36	4,663
10,001-50,000	$35.94	$57.64	70%	30%	$42.45	2,937
50,001-100,000	$37.52	$67.25	70%	30%	$46.44	445
> 100,000	$43.84	$71.85	70%	30%	$52.24	339

a. Source: Based on EPA WBS models. For more information, see USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"p1kUSUMx","properties":{"formattedCitation":"(2018g)","plainCitation":"(2018g)","noteIndex":0},"citationItems":[{"id":977,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":977,"type":"report","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
b. Calculated as technical wage rate times technical weight plus managerial wage rate times managerial weight.
c. Source: USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"parC4dj0","properties":{"formattedCitation":"(2018f)","plainCitation":"(2018f)","noteIndex":0},"citationItems":[{"id":923,"uris":["http://zotero.org/groups/945096/items/CW34PNAZ"],"uri":["http://zotero.org/groups/945096/items/CW34PNAZ"],"itemData":{"id":923,"type":"article","title":"Safe Drinking Water Information System Federal Reports Search","URL":"https://ofmpub.epa.gov/apex/sfdw/f?p=108:200::::::","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]},"accessed":{"date-parts":[["2018",8,28]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].
Includes community water systems.

For the systems serving more than 3,300, the EPA based the weight for technical and managerial labor on labor force data reported in [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"SBFUcslE","properties":{"formattedCitation":"(USEPA, 2009c)","plainCitation":"(USEPA, 2009c)","noteIndex":0},"citationItems":[{"id":924,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":924,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-

survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Comparing the managerial and treatment plant operator labor hours for all employment classes indicates that operator labor accounts for 70 percent of aggregate manager and operator labor hours while managerial hours account for 30 percent. Although the implied labor hour split was similar for smaller systems, the number of smaller systems reporting managerial hours was approximately one-third of those reporting treatment plant operator hours. Assuming one-third of systems serving up to 3,300 people have managers account for 30 percent of labor time, but the other two-thirds have no managerial labor time, the overall average is 10 percent managerial time.

The EPA calculated an overall weighted average wage rate across CWS based on the number of CWS in each size range. This yields an overall wage rate of $34.71 for PWSs. The EPA does not have wage rate data for NTNCWS. In the absence of data, the EPA used the CWS average wage rate as a proxy value for NTNCWS systems.

C.3 Household-Level Control Cost Calculations

This section shows how the EPA calculated household-level annual costs based on total annualized treatment costs. The analysis focuses on treatment costs because the cost of initial and follow-up monitoring will have a negligible impact on households.

First, the EPA estimated the number of households served by dividing PWS population by the median persons per household (PPH) for the service area associated with the PWS based on U.S. Census Bureau data. Then, the EPA summed treatment costs across all of a system's entry points and divided the total cost by the number of households. [REF _Ref534206622 \h] shows this calculation.

Exhibit [STYLEREF 5 \s]-[SEQ Table * ARABIC \s 5]: Calculation of Household-Level Annual Control Costs

Entry Point	PWS	PWS Pop[a]	PPH[b]	PWS Households[c]	Total Entry Point Annualized Cost[d]		Total PWS Annualized Cost[e]		Household Annual Cost[f]	
					3%	7%	3%	7%	3%	7%
MCL = 56 µg/L										
FL6280250_004_08004	FL6280250	38,761	2.67	14,517	$157,776	$200,214	$157,776	$200,214	$11	$14
PR0002702_2702004_00004	PR0002702	25,972	2.77	9,376	$644,017	$751,577	$644,017	$751,577	$69	$80
MCL = 18 µg/L										
FL6280250_001_08001	FL6280250	38,761	2.67	14,517	$197,908	$246,137	$630,485	$780,477	$43	$54
FL6280250_002_08002					$208,039	$257,730				
FL6280250_004_08004					$224,539	$276,611				
FL6411132_POE1_08001	FL6411132	198,500	2.67	74,345	$2,385,945	$2,710,362	$2,385,945	$2,710,362	$32	$36
GA2190000_323_15152	GA2190000	15,231	2.72	5,600	$142,776	$181,117	$142,776	$181,117	$25	$32
LA1089001_3CAA-6_00001T	LA1089001	24,081	2.62	9,191	$338,089	$403,270	$338,089	$403,270	$37	$44
MD0120001_0100000_00001	MD0120001	13,800	2.68	5,149	$199,068	$245,137	$199,068	$245,137	$39	$48
MD0120002_0100000_00001	MD0120002	12,002	2.68	4,478	$196,194	$241,914	$196,194	$241,914	$44	$54
MS0750005_7500502_00004T	MS0750005	4,309	2.65	1,626	$79,736	$103,513	$79,736	$103,513	$49	$64
NM3528616_003_00003	NM3528616	16,500	2.66	6,203	$111,127	$146,997	$111,127	$146,997	$18	$24
NV0000076_EP04_00206	NV0000076	220,000	2.70	81,481	$1,923,507	$2,187,850	$1,923,507	$2,187,850	$24	$27
OH0900715_EP001_00008	OH0900715	42,097	2.43	17,324	$347,464	$414,047	$347,464	$414,047	$20	$24
OH4401612_EP001_00006	OH4401612	25,091	2.43	10,326	$450,128	$529,521	$450,128	$529,521	$44	$51
OK2002412_UCM0001_11032	OK2002412	35,031	2.60	13,473	$563,740	$656,196	$563,740	$656,196	$42	$49
PA6200036_00101E_00100	PA6200036	16,000	2.47	6,478	$322,605	$386,584	$322,605	$386,584	$50	$60
PR0002702_2702004_00004	PR0002702	25,972	2.77	9,376	$677,224	$789,394	$677,224	$789,394	$72	$84

Entry Point	PWS	PWS Pop[a]	PPH[b]	PWS Households[c]	Total Entry Point Annualized Cost[d]		Total PWS Annualized Cost[e]		Household Annual Cost[f]	
TX1100002_04003_04003	TX1100002	13,805	2.88	4,793	$179,074	$222,667	$179,074	$222,667	$37	$46

a. PWS population based on USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"AxwMJrpi","properties":{"formattedCitation":"(2018d)","plainCitation":"(2018d)","noteIndex":0},"citationItems":[{"id":969,"uris":["http://zotero.org/groups/945096/items/YERQWPRZ"],"uri":["http://zotero.org/groups/945096/items/YERQWPRZ"],"itemData":{"id":969,"type":"article","title":"Perchlorate Occurrence and Monitoring Report","publisher":"EPA ***-*-**-***","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2018"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

b. Persons per household (PPH) is state-specific average household size from U.S. Census Bureau [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"i17uUQKL","properties":{"formattedCitation":"(2017c)","plainCitation":"(2017c)","noteIndex":0},"citationItems":[{"id":985,"uris":["http://zotero.org/groups/945096/items/CGU3LT9N"],"uri":["http://zotero.org/groups/945096/items/CGU3LT9N"],"itemData":{"id":985,"type":"article","title":"Average Household Size of Occupied Housing Units by Tenure. American Community Survey 1-Year Estimates: Table B25010","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2017"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

c. Calculated as PWS population divided by PPH.

d. Calculated based on method described in Section [REF _Ref523415174 \r \h].

e. Calculated as the sum of all entry point costs for the PWS; in cases where only one entry point incurs control costs, PWS costs equal entry point costs.

f. Calculated as total PWS annualized costs divided by PWS households.

United States
Environmental Protection
Agency

Best Available Technologies and Small System Compliance Technologies for Perchlorate in Drinking Water

Office of Water (4607M)
EPA ***-*-**-***
November 2018
www.epa.gov/safewater

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Table of Exhibits

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Abbreviations and Acronyms

AWWARF	American Water Works Research Foundation
BAT	best available technology
EBCT	empty bed contact time
EPA	Environmental Protection Agency
ESTCP	Environmental Security Technology Certification Program
GAC	granular activated carbon
MCL	maximum contaminant limit
MHI	median household income
MGD	million gallons per day
mg/L	milligrams per liter
NF	nanofiltration
O&M	operating and maintenance
POU	point-of-use
RO	reverse osmosis
SDWA	Safe Drinking Water Act
SSCT	small system compliance technology
UF	ultrafiltration
µg/L	micrograms per liter
WBS	Work Breakdown Structure

1 Introduction

The U.S. Environmental Protection Agency (EPA) is considering setting a federal maximum contaminant limit (MCL) for perchlorate in drinking water under the Safe Drinking Water Act (SDWA). This document addresses treatment technologies that drinking water systems could use to meet this potential new MCL. Specifically, it provides an evaluation of several technologies against predefined criteria to determine whether they might be considered best available technologies (BATs) to meet the potential MCL. In addition, it provides an evaluation of technologies for small systems against criteria to determine whether they can be designated small system compliance technologies (SSCT).

The three technologies included in the BAT evaluation are: ion exchange, biological treatment, and reverse osmosis (RO).[1] [REF _Ref330453648 * MERGEFORMAT] provides a list of the six major criteria considered for the BAT evaluation, along with specific evaluation questions. Sections [REF _Ref330470839 \r] through [REF _Ref525297841 \r \h] provide a discussion of the extent to which each technology meets the BAT criteria. Section [REF _Ref525297883 \r \h] provides a summary of the BAT evaluation results. The detailed discussion is based primarily on literature search information and technical analysis conducted during development of the document, *Technologies and Costs for Treating Perchlorate-Contaminated Water* [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ehEOwiCI","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":246,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":246,"type":"article","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. That document contains more complete description of each technology and the state of science regarding their use for perchlorate treatment.

The SDWA, as amended in 1996, requires that EPA list technologies for small systems [Section 1412(b)(4)(E)(ii)]:

> The Administrator shall include in the list any technology, treatment technique, or other means that is affordable, as determined by the Administrator in consultation with the States, for small public water systems serving -
>
> (I) a population of 10,000 or fewer but more than 3,300;
>
> (II) a population of 3,300 or fewer but more than 500; and
>
> (III) a population of 500 or fewer but more than 25;

[1] Granular activated carbon (GAC) is not included in this evaluation. Although there have been a few studies on the use of specially-modified GAC media for perchlorate removal, there have been no full-scale demonstrations of the technology and no apparent effort to certify the modified GAC media as safe for drinking water use.

and that achieves compliance with the MCL or treatment technique, including packaged or modular systems and point-of-entry or point-of-use treatment units (POU).

Section [REF _Ref330470934 \r] of this document provides EPA's analysis to identify SSCTs for the proposed rule. Specifically, it evaluates four technologies against the affordability and compliance effectiveness criteria for SSCTs. The technologies are the three included in the BAT analysis and POU reverse osmosis. EPA's affordability criterion uses an affordability threshold of 2.5 percent of the median household income (MHI) of the median water system (as ranked by MHI) in each small system size category (i.e., systems serving populations of (1) 25 – 500; (2) 501 – 3,300; and (3) 3,301 – 10,000 people). As long as the sum of baseline expenditures on water (i.e., current costs excluding perchlorate treatment costs) and the incremental expenditures associated with a particular perchlorate treatment technology do not exceed 2.5 percent of MHI, then that technology meets the affordability criterion.

Exhibit [SEQ Exhibit * ARABIC]. BAT Criteria for Perchlorate Technologies Evaluation

1. High Removal Efficiency
1.1. Have high removal efficiencies that achieve potential MCLs been documented?
1.2. Are the effects of water quality parameters on treatment effectiveness and reliability well-known?
1.3. Is the technology reliable enough to continuously meet a drinking water MCL?
1.4. Is additional research needed?
2. History of Full-Scale Operation
2.1. Do existing studies include full-scale operations at drinking water treatment facilities?
2.2. Are there studies of full-scale treatment of residuals that fully characterize residual waste streams and disposal options?
2.3. Can the bench or pilot studies be scaled up to represent full-scale treatment, including residuals generation and handling?
2.4. Is additional research needed?
3. General Geographic Applicability
3.1. What regions do the existing research studies represent?
3.2. Is it known that regional water quality variations will limit treatment effectiveness or reliability in some areas?
3.3. Are there any regional issues with respect to residuals handling or water resource use?
3.4. Is additional research needed?
4. Compatibility with Other Treatment Processes
4.1. Have the effects (adverse or beneficial) of the treatment process on other processes likely to be present at existing plants been evaluated?
4.2. Will additional pre- or post-treatment be required for integration into an existing (or planned) treatment train?
4.3. Is additional research needed?
5. Ability to Bring All of the Water System into Compliance
5.1. Will the treatment process adversely affect the distribution system or water resource decisions?
5.2. Might the treatment process, residuals handling, or pre- or post-treatment requirements raise new environmental quality concerns?
5.3. Is additional research needed?
6. Reasonable Cost Basis for Large and Medium Systems
6.1. Is the technology currently used by medium and large systems (including uses for other treatment purposes)?
6.2. Do the treatment studies provide sufficient information on design assumptions to allow cost modeling?
6.3. Is additional research needed?

2 Best Available Technology Evaluation for Ion Exchange

The State of California has identified ion exchange (along with fluidized bed biological treatment) as one of two BATs for achieving compliance with its standard for perchlorate in drinking water (CCR, Title 22, Chapter 15, Section 64447.2). Ion exchange is a physical/chemical separation process in which an ion (such as perchlorate) in the feed water is exchanged for an ion (typically chloride) on a resin generally made of synthetic beads or gel. A variety of resin types have been tested for perchlorate removal. These resin types include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base polyacrylic, weak-base polystyrenic, and perchlorate-selective.[2]

In application, feed water passes through a bed of resin in a vessel or column. The operation typically continues until the resin is exhausted, meaning that the chloride on enough of the resin's available exchange sites has been replaced with ions from the feed water that the resin is no longer effective for removing the ion. At this point, the resin may be disposed and replaced or regenerated. Based on data from full-scale operations (see below), it is likely that most systems using ion exchange to comply with a perchlorate MCL would use a perchlorate-selective resin that would be disposed, rather than regenerated, when exhausted. This resin choice has implications for technology feasibility, particularly with regard to residuals management, as discussed below.

2.1 High Removal Efficiency for Ion Exchange

2.1.1 Have high removal efficiencies that achieve potential MCLs been documented?

Yes. The literature documents perchlorate removal efficiencies for ion exchange that are typically in the high 90 percent range and to levels well below the potential MCLs, especially when using perchlorate-selective resin. This includes results from studies conducted in the laboratory, in the field at pilot scale, and in full-scale application. **[REF _Ref296588903 \h]** summarizes the removal efficiencies and resulting concentrations reported in the literature. Ion exchange with various types of resin is capable of removing perchlorate to levels below 4 micrograms per liter (µg/L), even given very high influent perchlorate concentrations. For perchlorate-selective resins, the research has shown that levels below 1 to 2 µg/L are achievable.

[2] While Tripp et al. (2003) also examined strong base polyvinylpyridine resins, comparable quantitative data on their removal efficiency are not available.

Exhibit [SEQ Exhibit * ARABIC]. Perchlorate Effectiveness Results for Ion Exchange

Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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	>75% to >80%	<2	L, P	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZOPJF1mT","properties":{"formattedCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006)","plainCitation":"(Blute, Seidel, McGuire, Qin, & Byerrum, 2006)","noteIndex":0},"citationItems":[{"id":987,"uris":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":987,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
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Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
				Technology & Regulatory Council (ITRC) Team"}],"issued":{"date-parts":[["2008",3]]},"accessed":{"date-parts":[["2018",10,13]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
	>96% to >99.7%	<4	L	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"hhUw3lq8","properties":{"formattedCitation":"(Ground-Water Remediation Technologies Analysis Center (GWRTAC), 2001)","plainCitation":"(Ground-Water Remediation Technologies Analysis Center (GWRTAC), 2001)","noteIndex":0},"citationItems":[{"id":1145,"uris":["http://zotero.org/groups/945096/items/EKWDU7IW"],"uri":["http://zotero.org/groups/945096/items/EKWDU7IW"],"itemData":{"id":1145,"type":"report","title":"Technology Status Report: Perchlorate Treatment Technologies, First Edition","collection-title":"Technology Status Report TS-01-01","author":[{"family":"Ground-Water Remediation Technologies Analysis Center (GWRTAC)","given":""}],"issued":{"date-parts":[["2001"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
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Notes:
1. SB = strong-base; SB-S = strong-base polystyrenic; SB-A = strong-base polyacrylic; WB-S = weak-base polystyrenic; WB-A = weak-base polyacrylic; NS = nitrate-selective strong-base polystyrenic; PS = perchlorate selective
2. L = laboratory study; P = field pilot study; F = full-scale

2.1.2 Are the effects of water quality parameters on treatment effectiveness and reliability well-known?

Yes. Effectiveness varies depending on water quality, but for perchlorate-selective resins the effect is limited. The most significant raw water quality consideration in ion exchange perchlorate treatment is the concentration of competing anions (particularly sulfate, nitrate, bicarbonate, and chloride). The effect of these anions is to decrease a resin's longer-term capacity to adsorb perchlorate, as they compete with perchlorate for exchange sites. There are significant differences among resin types in terms of the relative impact of competing anions. This impact is related to the relative affinity of the resin for each anion present. The order of affinity for perchlorate-selective resins is as follows [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"UTFMr5pk","properties":{"formattedCitation":"(Boodoo, 2003)","plainCitation":"(Boodoo, 2003)","noteIndex":0},"citationItems":[{"id":986,"uris":["http://zotero.org/groups/945096/items/2W4DAVDK"],"uri":["http://zotero.org/groups/945096/items/2W4DAVDK"],"itemData":{"id":986,"type":"article-journal","title":"POU/POE removal of perchlorate","container-title":"Water Conditioning and Purification","volume":"45","issue":"8","author":[{"family":"Boodoo","given":"F"}],"issued":{"date-parts":[["2003",8]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]:

perchlorate > nitrate > sulfate > chloride > bicarbonate.

In particular, the perchlorate affinity relative to nitrate affinity is nearly an order of magnitude greater [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"tVye3EEQ","properties":{"formattedCitation":"(Boodoo, 2003)","plainCitation":"(Boodoo, 2003)","noteIndex":0},"citationItems":[{"id":986,"uris":["http://zotero.org/groups/945096/items/2W4DAVDK"],"uri":["http://zotero.org/groups/945096/items/2W4DAVDK"],"itemData":{"id":986,"type":"article-journal","title":"POU/POE removal of perchlorate","container-title":"Water Conditioning and Purification","volume":"45","issue":"8","author":[{"family":"Boodoo","given":"F"}],"issued":{"date-parts":[["2003",8]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Although Boodoo [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"1GQXVrQv","properties":{"formattedCitation":"(2003)","plainCitation":"(2003)","noteIndex":0},"citationItems":[{"id":986,"uris":["http://zotero.org/groups/945096/items/2W4DAVDK"],"uri":["http://zotero.org/groups/945096/items/2W4DAVDK"],"itemData":{"id":986,"type":"article-journal","title":"POU/POE removal of perchlorate","container-title":"Water Conditioning and Purification","volume":"45","issue":"8","author":[{"family":"Boodoo","given":"F"}],"issued":{"date-parts":[["2003",8]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] suggests that perchlorate-selective resins would be negatively affected by high nitrate concentrations, a multitude of studies show that these resins are not, in fact, very sensitive to competing anions. Perchlorate capacity remains high for a wide range of nitrate and sulfate concentrations [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"KHtQdn9M","properties":{"formattedCitation":"(Blute et al.,

2006; Drago & Leserman, 2011; Gu et al., 1999; Gu, Brown, & Chiang, 2007; Gu et al., 2002; Lutes et al., 2010; J. Min, Boulos, & Brown, 2003; Russell et al., 2008; Tripp et al., 2003; Wu & Blute, 2010)","plainCitation":"(Blute et al., 2006; Drago & Leserman, 2011; Gu et al., 1999; Gu, Brown, & Chiang, 2007; Gu et al., 2002; Lutes et al., 2010; J. Min, Boulos, & Brown, 2003; Russell et al., 2008; Tripp et al., 2003; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":987,"uris":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":987,"type":"speech","title":"Bench and Pilot Testing of High Capacity, Single-Pass Ion Exchange Resins for Perchlorate Removal","publisher-place":"San Antonio, TX","event":"2006 AWWA Annual Conference & Exposition","event-place":"San Antonio, TX","author":[{"family":"Blute","given":"N.K."},{"family":"Seidel","given":"C.J."},{"family":"McGuire","given":"M.J."},{"family":"Qin","given":"D."},{"family":"Byerrum","given":"J."}],"issued":{"date-parts":[["2006",6]]}}},{"id":1161,"uris":["http://zotero.org/groups/945096/items/KIPNEQUM"],"uri":["http://zotero.org/groups/945096/items/KIPNEQUM"],"itemData":{"id":1161,"type":"paper-conference","title":"Castaic Lake Water Agency Operating Experience with Lead-Lag Anion Exchange for Perchlorate Removal","container-title":"Proceedings of the American Water Works Association Water Quality Technology Conference","event":"Water Quality Technology Conference","author":[{"family":"Drago","given":"J.A."},{"family":"Leserman","given":"J.R."}],"issued":{"date-parts":[["2011",11]]}}},{"id":1142,"uris":["http://zotero.org/groups/945096/items/A2TK7CI9"],"uri":["http://zotero.org/groups/945096/items/A2TK7CI9"],"itemData":{"id":1142,"type":"report","title":"Selective Anion Exchange Resins for the Removal of Perchlorate (ClO4) from Groundwater","collection-title":"Publication No. 4863. ORNL/TM-13753","publisher":"Oak Ridge National Laboratory, Environmental Sciences Division","publisher-place":"Oak Ridge, TN","event-place":"Oak Ridge, TN","author":[{"family":"Gu","given":"B."},{"family":"Brown","given":"G.M."},{"family":"Alexandratos","given":"S.D."},{"family":"Ober","given":"R."},{"family":"Patel","given":"V."}],"issued":{"date-parts":[["1999"]]}}},{"id":1144,"uris":["http://zotero.org/groups/945096/items/IBEDPSRF"],"uri":["http://zotero.org/groups/945096/items/IBEDPSRF"],"itemData":{"id":1144,"type":"article-journal","title":"Treatment of perchlorate-contaminated groundwater using highly selective, regenerable ion exchange technologies","container-title":"Environmental Science & Technology","page":"6277-6282","volume":"41","issue":"17","author":[{"family":"Gu","given":"B"},{"family":"Brown","given":"G.M."},{"family":"Chiang","given":"C.-C."}],"issued":{"date-parts":[["2007",9,1]]}}},{"id":1140,"uris":["http://zotero.org/groups/945096/items/NB3E2D3V"],"uri":["http://zotero.org/groups/945096/items/NB3E2D3V"],"itemData":{"id":1140,"type":"article-journal","title":"Treatment of perchlorate-contaminated groundwater using highly selective, regenerable ion-exchange technology: a pilot-scale demonstration","container-title":"Remediation","page":"51-68","volume":"12","issue":"2","author":[{"family":"Gu","given":"B."},{"family":"Ku","given":"Y.-K."},{"family":"Brown","given":"G.M."}],"issued":{"date-parts":[["2002",3,26]]}}},{"id":1028,"uris":["http://zotero.org/groups/945096/items/YGA3KSYS"],"uri":["http://zotero.org/groups/945096/items/YGA3KSYS"],"itemData":{"id":1028,"type":"report","title":"Final Report: Integrated Ion Exchange Regeneration Process for Drinking

Water","collection-title":"U.S. Department of Defense Environmental Security Technology Certification Prgoram (ESTCP). ESTCP Project ER-0545","author":[{"family":"Lutes","given":"C."},{"family":"Henderson","given":"T."},{"family":"Singer","given":"C."},{"family":"Garcia","given":"D."},{"family":"Pollack","given":"N."},{"family":"Chiang","given":"C."},{"family":"Gu","given":"B."}],"issued":{"date-parts":[["2010"]]}}},{"id":1117,"uris":["http://zotero.org/groups/945096/items/3VJGYCLC"],"uri":["http://zotero.org/groups/945096/items/3VJGYCLC"],"itemData":{"id":1117,"type":"report","title":"Process Train Selection: Membrane, Ion Exchange, Biological","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California Water Agencies","author":[{"family":"Min","given":"J."},{"family":"Boulos","given":"L."},{"family":"Brown","given":"J."}],"issued":{"date-parts":[["2003",4]]}}},{"id":1097,"uris":["http://zotero.org/groups/945096/items/NLAFHBV2"],"uri":["http://zotero.org/groups/945096/items/NLAFHBV2"],"itemData":{"id":1097,"type":"speech","title":"Pilot Testing of Single Pass Perchlorate-Selective Ion Exchange Resins at Three Utilities in the Main San Gabriel Basin","publisher-place":"Cincinnati, OH","event":"AWWA Water Quality Technology Conference & Exposition","event-place":"Cincinnati, OH","author":[{"family":"Russell","given":"C.G."},{"family":"Qin","given":"G."},{"family":"Blute","given":"N.K."},{"family":"McGuire","given":"M.J."},{"family":"Williams","given":"C."}],"issued":{"date-parts":[["2008",11]]}}},{"id":1013,"uris":["http://zotero.org/groups/945096/items/J24BWNQH"],"uri":["http://zotero.org/groups/945096/items/J24BWNQH"],"itemData":{"id":1013,"type":"article","title":"Treatment of perchlorate in groundwater by ion exchange technology","publisher":"AWWA Research Foundation","call-number":"Publication No. 909","author":[{"family":"Tripp","given":"A.R."},{"family":"Clifford","given":"D."},{"family":"Roberts","given":"D.J."},{"family":"Cang","given":"Y."},{"family":"Aldridge","given":"L."},{"family":"Gillogly","given":"T."},{"family":"Boulos","given":"L."}],"issued":{"date-parts":[["2003"]]}}},{"id":1058,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1058,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Although most investigators identify bicarbonate and chloride as other major competing anions, the affinity of ion exchange resins, particularly perchlorate-selective resins, for these anions is less than that for perchlorate, sulfate, and nitrate. Therefore, their impact on resin perchlorate capacity would be expected to be less than that of sulfate and nitrate. There are, however, no quantitative data in the literature on the effects of these major anions. Other co-contaminants that may affect perchlorate capacity include arsenic [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"WcuhRWxg","properties":{"formattedCitation":"(Berlien, 2003; Tripp et al., 2003)","plainCitation":"(Berlien, 2003; Tripp et al., 2003)","noteIndex":0},"citationItems":[{"id":992,"uris":["http://zotero.org/groups/945096/items/8PB22K95"],"uri":["http://zotero.org/groups/945096/items/8PB22K95"],"itemData":{"id":992,"type":"report","title":"La Puente Valley County Water District's Experience with ISEP","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California

Water Agencies","author":[{"family":"Berlien","given":"M.J."}],"issued":{"date-parts":[["2003",4]]}}},{"id":1013,"uris":["http://zotero.org/groups/945096/items/J24BWNQH"],"uri":["http://zotero.org/groups/945096/items/J24BWNQH"],"itemData":{"id":1013,"type":"article","title":"Treatment of perchlorate in groundwater by ion exchange technology","publisher":"AWWA Research Foundation","call-number":"Publication No. 909","author":[{"family":"Tripp","given":"A.R."},{"family":"Clifford","given":"D."},{"family":"Roberts","given":"D.J."},{"family":"Cang","given":"Y."},{"family":"Aldridge","given":"L."},{"family":"Gillogly","given":"T."},{"family":"Boulos","given":"L."}],"issued":{"date-parts":[["2003"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], uranium [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"HOxGLk5E","properties":{"formattedCitation":"(J. Min et al., 2003; Tripp et al., 2003)","plainCitation":"(J. Min et al., 2003; Tripp et al., 2003)","noteIndex":0},"citationItems":[{"id":1117,"uris":["http://zotero.org/groups/945096/items/3VJGYCLC"],"uri":["http://zotero.org/groups/945096/items/3VJGYCLC"],"itemData":{"id":1117,"type":"report","title":"Process Train Selection: Membrane, Ion Exchange, Biological","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California Water Agencies","author":[{"family":"Min","given":"J."},{"family":"Boulos","given":"L."},{"family":"Brown","given":"J."}],"issued":{"date-parts":[["2003",4]]}}},{"id":1013,"uris":["http://zotero.org/groups/945096/items/J24BWNQH"],"uri":["http://zotero.org/groups/945096/items/J24BWNQH"],"itemData":{"id":1013,"type":"article","title":"Treatment of perchlorate in groundwater by ion exchange technology","publisher":"AWWA Research Foundation","call-number":"Publication No. 909","author":[{"family":"Tripp","given":"A.R."},{"family":"Clifford","given":"D."},{"family":"Roberts","given":"D.J."},{"family":"Cang","given":"Y."},{"family":"Aldridge","given":"L."},{"family":"Gillogly","given":"T."},{"family":"Boulos","given":"L."}],"issued":{"date-parts":[["2003"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and chromium [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"AbXppyV6","properties":{"formattedCitation":"(J. Min et al., 2003)","plainCitation":"(J. Min et al., 2003)","noteIndex":0},"citationItems":[{"id":1117,"uris":["http://zotero.org/groups/945096/items/3VJGYCLC"],"uri":["http://zotero.org/groups/945096/items/3VJGYCLC"],"itemData":{"id":1117,"type":"report","title":"Process Train Selection: Membrane, Ion Exchange, Biological","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California Water Agencies","author":[{"family":"Min","given":"J."},{"family":"Boulos","given":"L."},{"family":"Brown","given":"J."}],"issued":{"date-parts":[["2003",4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Based on the high affinity of most resins for perchlorate, direct competition from these co-contaminants would be expected to be low.

2.1.3 Is the technology reliable enough to continuously meet a drinking water MCL?

Yes. Numerous full-scale drinking water facilities are using ion exchange to meet the State of California's MCL for perchlorate (see Question [REF _Ref525556890 \r \h], below). In general,

ion exchange is an established, reliable technology that has been used successfully to meet other MCLs.

2.1.4 Is additional research needed?

No. Additional research is not required.

2.2 History of Full-Scale Operation for Ion Exchange

2.2.1 Do existing studies include full-scale operations at drinking water treatment facilities?

Yes. The literature identifies 44 full-scale facilities applying ion exchange for perchlorate removal [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Db8Iyu4N","properties":{"formattedCitation":"(USEPA, 2018)","plainCitation":"(USEPA, 2018)","noteIndex":0},"citationItems":[{"id":246,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":246,"type":"article","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-****","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Many of these facilities are drinking water treatment facilities. With the majority of these facilities located in California, the full-scale use of the technology appears to be focused on compliance with that State's MCL for perchlorate.

The data on full-scale facilities demonstrate the increasing use of perchlorate-selective resins. Currently, more than half of the identified full-scale facilities (18 of 23 facilities where information on resin type is available) use perchlorate-selective resins. An additional two facilities are reportedly planning to switch to perchlorate-selective resin [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8nzutk01","properties":{"formattedCitation":"(Blute, 2012; Wu & Blute, 2010)","plainCitation":"(Blute, 2012; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":988,"uris":["http://zotero.org/groups/945096/items/IRPKNW73"],"uri":["http://zotero.org/groups/945096/items/IRPKNW73"],"itemData":{"id":988,"type":"report","title":"Comments submitted during External Expert Review of the Perchlorate Technologies and Cost Document","author":[{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2012",12]]}}},{"id":1058,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1058,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Thus, perchlorate-selective resin appears to have become the technology of choice for perchlorate ion exchange facilities.

2.2.2 Are there studies of full-scale treatment of residuals that fully characterize residual waste streams and disposal options?

Yes. Almost 79 percent (30 of 38) of the full-scale perchlorate ion exchange facilities for which waste management data are available operate on a throwaway basis. This statistic includes all but one of the full-scale facilities using perchlorate-selective resin. An additional two facilities are reportedly planning to switch away from regeneration to disposal of spent resin [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"83c3WTYX","properties":{"formattedCitation":"(Blute, 2012; Wu & Blute, 2010)","plainCitation":"(Blute, 2012; Wu & Blute, 2010)","noteIndex":0},"citationItems":[{"id":988,"uris":["http://zotero.org/groups/945096/items/IRPKNW73"],"uri":["http://zotero.org/groups/945096/items/IRPKNW73"],"itemData":{"id":988,"type":"report","title":"Comments submitted during External Expert Review of the Perchlorate Technologies and Cost Document","author":[{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2012",12]]}}},{"id":1058,"uris":["http://zotero.org/groups/945096/items/2QPEXW23"],"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1058,"type":"speech","title":"Perchlorate Removal Using Single-Pass Ion Exchange Resin - Pilot Testing Purolite A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010 California-Nevada AWWA Spring Conference","event-place":"Hollywood, CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"date-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. These systems generate solid waste in the form of spent resin loaded with perchlorate and other anions. The facilities that operate with resin regeneration are older facilities. New facilities installed to comply with a perchlorate MCL would be unlikely to adopt this mode of operation.

The primary concern with spent resin is that hazardous co-contaminants (such as arsenic, uranium, and chromium) might accumulate on the resin. For example, Tripp et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"LTmBSWYw","properties":{"formattedCitation":"(2003)","plainCitation":"(2003)","noteIndex":0},"citationItems":[{"id":1013,"uris":["http://zotero.org/groups/945096/items/J24BWNQH"],"uri":["http://zotero.org/groups/945096/items/J24BWNQH"],"itemData":{"id":1013,"type":"article","title":"Treatment of perchlorate in groundwater by ion exchange technology","publisher":"AWWA Research Foundation","call-number":"Publication No. 909","author":[{"family":"Tripp","given":"A.R."},{"family":"Clifford","given":"D."},{"family":"Roberts","given":"D.J."},{"family":"Cang","given":"Y."},{"family":"Aldridge","given":"L."},{"family":"Gillogly","given":"T."},{"family":"Boulos","given":"L."}],"issued":{"date-parts":[["2003"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] suggest that a perchlorate-selective resin would require frequent disposal to prevent arsenic and uranium build-up. Recent studies of various perchlorate-selective resins, however, have shown that build-up of metals results in concentrations that are below regulatory limits that would require disposal as a hazardous waste, both under federal requirements and California's more stringent limits [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"VVmZ1vIM","properties":{"formattedCitation":"(Blute et al., 2006; Russell et al., 2008; Wu & Blute, 2010)","plainCitation":"(Blute et al., 2006; Russell et al., 2008; Wu &

Blute,
2010)","noteIndex":0},"citationItems":[{"id":987,"uris":["http://zotero.org/groups/945096/items/
8Z7K9ZUJ"],"uri":["http://zotero.org/groups/945096/items/8Z7K9ZUJ"],"itemData":{"id":987,"
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,"uri":["http://zotero.org/groups/945096/items/2QPEXW23"],"itemData":{"id":1058,"type":"spe
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A532E at the San Gabriel B6 Plant","publisher-place":"Hollywood, CA","event":"2010
California-Nevada AWWA Spring Conference","event-place":"Hollywood,
CA","author":[{"family":"Wu","given":"X."},{"family":"Blute","given":"N.K."}],"issued":{"dat
e-parts":[["2010",3,31]]}}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"}]. The same studies found that uranium build-up might require special handling as a radioactive waste in only one of the 12 samples tested (total across all three studies).

Because of the shorter life of conventional (not perchlorate-selective) resins, metals accumulation in these resins likely would be even lower and, thus, the same result should hold true (although few full-scale systems would be expected to use these resins). A number of studies are also available characterizing spent regenerant [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Hf5RObPs","properties":{"formattedCitation":"(Batista et al., 2003; Berlien,
2003; Case et al., 2004; Gu et al., 2002; Lutes et al., 2010; Montgomery Watson Harza (MWH)
and University of Houston, 2003)","plainCitation":"(Batista et al., 2003; Berlien, 2003; Case et
al., 2004; Gu et al., 2002; Lutes et al., 2010; Montgomery Watson Harza (MWH) and University
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2003)","noteIndex":0},"citationItems":[{"id":993,"uris":["http://zotero.org/groups/945096/items/
5MCR8IMA"],"uri":["http://zotero.org/groups/945096/items/5MCR8IMA"],"itemData":{"id":99
3,"type":"article-journal","title":"Combining Ion-Exchange (IX) Technology and Biological
Reduction for Perchlorate Removal","container-title":"Remediation","page":"21-
38","volume":"13","issue":"1","author":[{"family":"Batista","given":"J.R."},{"family":"Gingras
","given":"T.M."},{"family":"Vieira","given":"A.R."}],"issued":{"date-
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title":"La Puente Valley County Water District's Experience with ISEP","collection-
title":"Presentation of Carollo Engineers, Inc. and Association of California Water

Agencies","author":[{"family":"Berlien","given":"M.J."}],"issued":{"date-parts":[["2003",4]]}}},{"id":1173,"uris":["http://zotero.org/groups/945096/items/3I3ZVUFE"],"uri":["http://zotero.org/groups/945096/items/3I3ZVUFE"],"itemData":{"id":1173,"type":"report","title":"Perchlorate Research Partnership - Overview and Technology Review","publisher":"American Water Works Association Research Foundatoin","publisher-place":"Denver, CO","event-place":"Denver, CO","author":[{"family":"Case","given":"T."},{"family":"Cannon","given":"F."},{"family":"Clifford","given":"D."},{"family":"Rittman","given":"B."},{"family":"Logan","given":"B."},{"family":"Evans","given":"P."},{"family":"Adham","given":"S."},{"family":"Aldridge","given":"L."}],"issued":{"date-parts":[["2004"]]}}},{"id":1140,"uris":["http://zotero.org/groups/945096/items/NB3E2D3V"],"uri":["http://zotero.org/groups/945096/items/NB3E2D3V"],"itemData":{"id":1140,"type":"article-journal","title":"Treatment of perchlorate-contaminated groundwater using highly selective, regenerable ion-exchange technology: a pilot-scale demonstration","container-title":"Remediation","page":"51-68","volume":"12","issue":"2","author":[{"family":"Gu","given":"B."},{"family":"Ku","given":"Y.-K."},{"family":"Brown","given":"G.M."}],"issued":{"date-parts":[["2002",3,26]]}}},{"id":1028,"uris":["http://zotero.org/groups/945096/items/YGA3KSYS"],"uri":["http://zotero.org/groups/945096/items/YGA3KSYS"],"itemData":{"id":1028,"type":"report","title":"Final Report: Integrated Ion Exchange Regeneration Process for Drinking Water","collection-title":"U.S. Department of Defense Environmental Security Technology Certification Prgoram (ESTCP). ESTCP Project ER-0545","author":[{"family":"Lutes","given":"C."},{"family":"Henderson","given":"T."},{"family":"Singer","given":"C."},{"family":"Garcia","given":"D."},{"family":"Pollack","given":"N."},{"family":"Chiang","given":"C."},{"family":"Gu","given":"B."}],"issued":{"date-parts":[["2010"]]}}},{"id":1116,"uris":["http://zotero.org/groups/945096/items/WU4Z87VI"],"uri":["http://zotero.org/groups/945096/items/WU4Z87VI"],"itemData":{"id":1116,"type":"report","title":"Treatibility of Perchlorate in Groundwater Using Ion-Exchange Technology","collection-title":"Project 2805, Phase II, Progress Report No. 4","publisher":"AWWA Research Foundation","publisher-place":"Denver, CO","event-place":"Denver, CO","author":[{"literal":"Montgomery Watson Harza (MWH) and University of Houston"}],"issued":{"date-parts":[["2003"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Again though, few full-scale systems would be expected to operate with resin regeneration.

2.2.3 Can the bench or pilot studies be scaled up to represent full-scale treatment, including residuals generation and handling?

Yes. As a mature and established technology, the scale-up of ion exchange, in general, from bench- to pilot- to full-scale is well understood.

2.2.4 Is additional research needed?

No. Additional research is not required.

2.3 General Geographic Applicability for Ion Exchange

2.3.1 What regions do the existing research areas represent?

Studies of ion exchange treatment of perchlorate have primarily been conducted in California and Nevada. For perchlorate-selective resin in particular, most recent studies have used water that is representative of those areas.

2.3.2 Is it known that regional water quality variations will limit treatment effectiveness or reliability in some areas?

No. Although most of the existing research is for a limited region, there are no data indicating that regional water quality variations will limit effectiveness or reliability. Given that the effect of source water quality parameters on perchlorate-selective resin is limited (see Question [REF _Ref525290149 \r \h]), source water conditions in other regions are not likely to have a substantial impact.

2.3.3 Are there any regional issues with respect to residuals handling or water resource use?

There are regions where disposal of spent regenerant would be an issue. Few full-scale systems, however, would be expected to operate with resin regeneration. Regional barriers are not anticipated with respect to spent resin disposal unless co-occurring contaminants that accumulate on the resin are classified as hazardous or radioactive (see Question [REF _Ref525289868 \r \h]).

2.3.4 Is additional research needed?

No. Additional research is not required.

2.4 Compatibility of Ion Exchange with Other Treatment Processes

2.4.1 Have the effects (adverse or beneficial) of the treatment process on other processes likely to be present at existing plants been evaluated?

Yes. Ion exchange can have an adverse effect on treated water chemistry by increasing corrosivity (see Question [REF _Ref525290744 \r \h]). The technology can also have a beneficial effect by removing other undesirable anions from the treated water (e.g., arsenic, uranium), even when using perchlorate-selective resin (see Questions [REF _Ref525290149 \r \h] and [REF _Ref525289868 \r \h]).

2.4.2 Will additional pre- or post-treatment be required for integration into an existing (or planned) treatment train?

Possibly. The treated water chemistry changes resulting from ion exchange might require post-treatment corrosion control or alter existing corrosion control or disinfection requirements.

2.4.3 Is additional research needed?

No. Additional research is not required.

2.5 Ability of Ion Exchange to Bring all of the Water System into Compliance

2.5.1 Will the treatment process adversely affect the distribution system or water resource decisions?

Ion exchange treatment can increase the corrosivity of treated water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"CZf30VJz","properties":{"formattedCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005)","plainCitation":"(Berlien, 2003; Betts, 1998; USEPA, 2005)","noteIndex":0},"citationItems":[{"id":992,"uris":["http://zotero.org/groups/945096/items/8PB22K95"],"uri":["http://zotero.org/groups/945096/items/8PB22K95"],"itemData":{"id":992,"type":"report","title":"La Puente Valley County Water District's Experience with ISEP","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California Water Agencies","author":[{"family":"Berlien","given":"M.J."}],"issued":{"date-parts":[["2003",4]]}}},{"id":991,"uris":["http://zotero.org/groups/945096/items/BNWD5VQP"],"uri":["http://zotero.org/groups/945096/items/BNWD5VQP"],"itemData":{"id":991,"type":"article-journal","title":"Rotation ion-exchange system removes perchlorate","page":"454A-455A","volume":"32","journalAbbreviation":"Environ. Sci. Technol.","author":[{"family":"Betts","given":"K.S."}],"issued":{"date-parts":[["1998"]]}}},{"id":1046,"uris":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"uri":["http://zotero.org/groups/945096/items/EWAQ4GEK"],"itemData":{"id":1046,"type":"article","title":"Perchlorate Treatment Technology Update: Federal Facilities Forum Issue Paper","publisher":"Office of Solid Waste and Emergency Response. EPA 542-R-05-015","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] because of the addition of chloride ions and/or removal of carbonates and bicarbonates. Berlien [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"v50fvsPm","properties":{"formattedCitation":"(2003)","plainCitation":"(2003)","noteIndex":0},"citationItems":[{"id":992,"uris":["http://zotero.org/groups/945096/items/8PB22K95"],"uri":["http://zotero.org/groups/945096/items/8PB22K95"],"itemData":{"id":992,"type":"report","title":"La Puente Valley County Water District's Experience with ISEP","collection-title":"Presentation of Carollo Engineers, Inc. and Association of California Water Agencies","author":[{"family":"Berlien","given":"M.J."}],"issued":{"date-parts":[["2003",4]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] reports this problem with a full-scale application of ion exchange for perchlorate treatment. Treated water had a pH of approximately 7 and created red water problems in older homes with galvanized steel pipe. The operators corrected this problem by adding sodium hydroxide to raise the pH to approximately 8.2 and adding polyphosphates as an additional protection measure. Thus, distribution system effects can be managed by adjusting corrosion control programs.

The potentially large volume of spent regenerant could be a barrier in regions with water resource issues. Few full-scale systems, however, would be expected to operate with resin regeneration.

2.5.2 Might the treatment process, residuals handling, or pre- or post-treatment requirements raise new environmental quality concerns?

The disposal of large volumes of spent regenerant could create an environmental quality concern. Few full-scale systems, however, would be expected to operate with resin regeneration.

2.5.3 Is additional research needed?

No. Additional research is not required.

2.6 Reasonable Cost Basis for Ion Exchange for Large and Medium Systems

2.6.1 Is the technology currently used by medium and large systems (including uses for other treatment purposes)?

Yes. The 44 full-scale perchlorate ion exchange systems identified in the literature include a number of medium and large systems: 31 are larger than 1 million gallons per day (MGD) and six are larger than 10 MGD, with the largest being 14.4 MGD.

2.6.2 Do the treatment studies provide sufficient information for design assumptions to allow cost modeling?

Detailed data are available from the treatment studies for all of the relevant design parameters, including:

- Resin type
- Vessel configuration (i.e., number of vessels in series)
- Empty bed contact time (EBCT)
- Resin bed life
- Surface loading rate
- Regeneration parameters.

2.6.3 Is additional research needed?

No. Additional research is not required.

3 Best Available Technology Evaluation for Biological Treatment

The State of California has identified biological treatment (along with ion exchange) as one of two BATs for achieving compliance with its standard for perchlorate in drinking water (CCR, Title 22, Chapter 15, Section 64447.2). Biological treatment of perchlorate is the process by which bacteria are used to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. The process typically involves the addition of an oxidizable substrate (also referred to as the electron donor or "food"), such as acetate or ethanol. Biological treatment offers complete destruction of the perchlorate ion, eliminating the need for management of perchlorate-bearing waste streams.

The most promising designs for biological treatment of perchlorate at drinking water facilities are those that operate either in a fixed bed or a fluidized bed configuration. Both fixed bed and fluidized bed designs involve a media bed that provides a surface on which perchlorate-reducing bacteria grows. For fixed bed reactors, influent water is typically passed under pressure through a static media bed located in a vessel. An alternative fixed bed design uses a gravity-fed concrete basin to hold the biologically active media. Fluidized bed bioreactor designs use vessels where high influent rates in an up-flow design fluidize the media bed allowing for more surface area for biomass growth. California's BAT for perchlorate specifies fluidized bed biological treatment.

3.1 High Removal Efficiency for Biological Treatment

3.1.1 Have high removal efficiencies that achieve potential MCLs been documented?

Yes. [REF _Ref297622446 \h * MERGEFORMAT] summarizes the removal efficiencies and resulting concentrations reported in the literature. It shows that fixed and fluidized bed reactors have consistently achieved removal efficiencies greater than 90 percent, reducing perchlorate to levels that are usually below detection limits of 4 µg/L or lower, even given very high influent perchlorate concentrations. Most of the data in the exhibit are from laboratory-, pilot-, and field-scale tests of biological treatment. Also included, however, are data from several full-scale treatment systems.

Exhibit [SEQ Exhibit * ARABIC]. Perchlorate Effectiveness Results for Biological Treatment

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
>99%	<4	Bench-scale fixed bed	None	Sand / Acetate	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"4MElBxIB","properties":{"formattedCitation":"(Kim & Logan, 2000)","plainCitation":"(Kim & Logan, 2000)","noteIndex":0},"citationItems":[{"id":1135,"uris":["http://zotero.org/groups/945096/items/G9LNRV7T"],"uri":["http://zotero.org/groups/945096/items/G9LNRV7T"],"itemData":{"id":1135,"type":"article-journal","title":"Fixed-bed bioreactor treating perchlorate-contaminated waters","container-title":"Environmental Engineering Science","volume":"17","issue":"5","author":[{"family":"Kim","given":"K."},{"family":"Logan","given":"B.E."}],"issued":{"date-parts":[["2000"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>99%	<4	Bench-scale fixed bed	Nitrate (0.02), sulfate (0.04)	Celite / Acetate	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"95JFe0tq","properties":{"formattedCitation":"(Losi, Giblin, Hosangadi, & Frankenberger, 2002)","plainCitation":"(Losi, Giblin, Hosangadi, & Frankenberger, 2002)","noteIndex":0},"citationItems":[{"id":1125,"uris":["http://zotero.org/groups/945096/items/PYWQUJ5P"],"uri":["http://zotero.org/groups/945096/items/PYWQUJ5P"],"itemData":{"id":1125,"type":"article-journal","title":"Bioremediation of perchlorate-contaminated groundwater using a packed bed

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					biological reactor","container-title":"Bioremediation Journal","page":"97-104","volume":"6","issue":"2","author":[{"family":"Losi","given":"M.E."},{"family":"Giblin","given":"T."},{"family":"Hosangadi","given":"V."},{"family":"Frankenberger","given":"W.T."}],"issued":{"date-parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>98%	<3	Bench-scale fixed bed	Nitrate (13), sulfate (9.3 to16.8)	GAC / Acetic acid or proprietary carbohydrate solution	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"XsXEUMJv","properties":{"formattedCitation":"(Upadhyaya, Kotlarz, Togna, & Raskin, 2015)","plainCitation":"(Upadhyaya, Kotlarz, Togna, & Raskin, 2015)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1071,"uris":["http://zotero.org/groups/945096/items/KLWCLIE4"],"uri":["http://zotero.org/groups/945096/items/KLWCLIE4"],"itemData":{"id":1071,"type":"article-journal","title":"Carbohydrate-Based Electron Donor for Biological Nitrate and Perchlorate Removal From Drinking Water","container-title":"Journal - American Water Works Association","page":"E674-E684","volume":"107","issue":"12","source":"Wiley Online Library","abstract":"This study evaluated the feasibility of replacing acetic acid with a commercial carbohydrate-based electron donor (CBED) for removal of nitrate and perchlorate (ClO4–) from drinking water. Bench-scale biologically active carbon fixed-bed and fluidized-bed reactors (FXBR and FLBR,

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					respectively), with an initial empty bed contact time (EBCT) of 42.8 min, were fed simulated groundwater containing 15 mg/L nitrate as nitrogen and 200 µg/L ClO4–. EBCT in the FLBR after final expansion was 80.5 min. During the first 100 days using acetic acid at 125 mg/L chemical oxygen demand (COD), complete nitrate removal was achieved in both systems, whereas perchlorate in the FXBR and FLBR effluents remained below 3 and 6 µg/L ClO4–, respectively. For comparable removals, influent COD requirement was higher with the CBED. Biomass yields with acetic acid and the CBED were 0.54–0.58 and 0.59–0.74 mg CODbiomass/mg CODsubstrate, respectively. The higher yield with the CBED resulted in more frequent maintenance requirements.","DOI":"10.5942/jawwa.2015.107.0143","ISSN":"1551-8833","language":"en","author":[{"family":"Upadhyaya","given":"Giridhar"},{"family":"Kotlarz","given":"Nadine"},{"family":"Togna","given":"Paul"},{"family":"Raskin","given":"Lutgarde"}],"issued":{"date-parts":[["2015",12,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>94%	<4	Bench-scale fixed bed	Nitrate (4)	Sand, plastic media / Acetic acid	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"qPM4HxKc","properties":{"formattedCitation":"(Case et al., 2004; B. Min, Evans, Chu, & Logan, 2004)","plainCitation":"(Case et al., 2004; B. Min, Evans, Chu, & Logan,

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					2004)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1173,"uris":["http://zotero.org/groups/945096/items/3I3ZVUFE"],"uri":["http://zotero.org/groups/945096/items/3I3ZVUFE"],"itemData":{"id":1173,"type":"report","title":"Perchlorate Research Partnership - Overview and Technology Review","publisher":"American Water Works Association Research Foundation","publisher-place":"Denver, CO","event-place":"Denver, CO","author":[{"family":"Case","given":"T."},{"family":"Cannon","given":"F."},{"family":"Clifford","given":"D."},{"family":"Rittman","given":"B."},{"family":"Logan","given":"B."},{"family":"Evans","given":"P."},{"family":"Adham","given":"S."},{"family":"Aldridge","given":"L."}],"issued":{"date-parts":[["2004"]]}}},{"id":1118,"uris":["http://zotero.org/groups/945096/items/VTV55N8F"],"uri":["http://zotero.org/groups/945096/items/VTV55N8F"],"itemData":{"id":1118,"type":"article-journal","title":"Perchlorate removal in sand and plastic media bioreactors","container-title":"Water Research","page":"47-60","volume":"38","issue":"1","source":"PubMed","abstract":"The treatment of perchlorate-contaminated groundwater was examined using two side-by-side pilot-scale fixed-bed bioreactors packed with sand or plastic media, and bioaugmented with the perchlorate-degrading bacterium Dechlorosoma sp. KJ. Groundwater containing perchlorate (77microg/L),

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					nitrate (4mg-NO(3)/L), and dissolved oxygen (7.5mg/L) was amended with a carbon source (acetic acid) and nutrients (ammonium phosphate). Perchlorate was completely removed (<4microg/L) in the sand medium bioreactor at flow rates of 0.063-0.126L/s (1-2gpm or hydraulic loading rate of 0.34-0.68L/m(2)s) and in the plastic medium reactor at flow rates of <0.063L/s. Acetate in the sand reactor was removed from 43+/-8 to 13+/-8mg/L (after day 100), and nitrate was completely removed in the reactor (except day 159). A regular (weekly) backwashing cycle was necessary to achieve consistent reactor performance and avoid short-circuiting in the reactors. For example, the sand reactor detention time was 18min (hydraulic loading rate of 0.68L/m(2)s) immediately after backwashing, but it decreased to only 10min 1 week later. In the plastic medium bioreactor, the relative changes in detention time due to backwashing were smaller, typically changing from 60min before backwashing to 70min after backwashing. We found that detention times necessary for complete perchlorate removal were more typical of those expected for mixed cultures (10-18min) than those for the pure culture (<1min) reported in our previous laboratory studies. Analysis of intra-column perchlorate profiles revealed that there was simultaneous removal of dissolved oxygen, nitrate, and perchlorate, and that oxygen and nitrate

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					removal was always complete prior to complete perchlorate removal. This study demonstrated for the first time in a pilot-scale system, that with regular backwashing cycles, fixed-bed bioreactors could be used to remove perchlorate in groundwater to a suitable level for drinking water.","DOI":"10.1016/j.watres.2003.09.019","ISSN":"0043-1354","note":"PMID: 14630102","journalAbbreviation":"Water Res.","language":"eng","author":[{"family":"Min","given":"Booki"},{"family":"Evans","given":"Patrick J."},{"family":"Chu","given":"Allyson K."},{"family":"Logan","given":"Bruce E."}],"issued":{"date-parts":[["2004",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>93%	<5	Full-scale fixed bed[1]	Nitrate	GAC / Acetic acid	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"MzwlaxyZ","properties":{"formattedCitation":"(U.S. Department of Defense (U.S. DoD), 2008a)","plainCitation":"(U.S. Department of Defense (U.S. DoD), 2008a)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1074,"uris":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"uri":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"itemData":{"id":1074,"type":"report","title":"Direct Fixed-bed Biological Perchlorate Destruction Demonstration","genre":"ESTCP Final Report (ER-0544)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					parts":[["2008",9,25]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>92%	<4	Bench-scale fixed bed	Sulfate (0 to 220)	GAC/ Acetate or ethanol	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rISAf9UG","properties":{"formattedCitation":"(Brown, Snoeyink, Raskin, & Lin, 2003)","plainCitation":"(Brown, Snoeyink, Raskin, & Lin, 2003)","noteIndex":0},"citationItems":[{"id":984,"uris":["http://zotero.org/groups/945096/items/FFPYJC8D"],"uri":["http://zotero.org/groups/945096/items/FFPYJC8D"],"itemData":{"id":984,"type":"article-journal","title":"The sensitivity of fixed-bed biological perchlorate removal to changes in operating conditions and water quality characteristics","container-title":"Water Research","page":"206-214","volume":"37","issue":"1","author":[{"family":"Brown","given":"J.C."},{"family":"Snoeyink","given":"V.L."},{"family":"Raskin","given":"L"},{"family":"Lin","given":"R"}],"issued":{"date-parts":[["2003"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
92% to 99%	<4	Field-scale fixed bed[4]	Sulfate (140 to 250), Nitrate (6 to 29), DO (4 to 8)	GAC / Acetic acid	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"B5AvYc5U","properties":{"formattedCitation":"(Brown et al., 2005; The Interstate Technology & Regulatory Council (ITRC) Team, 2008)","plainCitation":"(Brown et al., 2005; The Interstate Technology & Regulatory Council (ITRC) Team, 2008)","noteIndex":0},"citatio

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					nItems":[{"id":983,"uris":["http://zotero.org/groups/945096/items/L8HMQ8VP"],"uri":["http://zotero.org/groups/945096/items/L8HMQ8VP"],"itemData":{"id":983,"type":"article-journal","title":"Fixed-bed biological treatment of perchlorate-contaminated drinking water","container-title":"Journal AWWA","volume":"97","issue":"9","author":[{"family":"Brown","given":"J.C."},{"family":"Anderson","given":"R.D."},{"family":"Min","given":"J.H."},{"family":"Boulos","given":"L."},{"family":"Prasifka","given":"D."},{"family":"Juby","given":"G.J.G."}],"issued":{"date-parts":[["2005"]]}}},{"id":1083,"uris":["http://zotero.org/groups/945096/items/5PV8GPIA"],"uri":["http://zotero.org/groups/945096/items/5PV8GPIA"],"itemData":{"id":1083,"type":"article","title":"Technical/Regulatory Guidance: Remediation Technologies for Perchlorate Contamination in Water and Soil","URL":"http://www.eosremediation.com/download/Perchlorate/ITRC%20PERC-2.pdf","author":[{"literal":"The Interstate Technology & Regulatory Council (ITRC) Team"}],"issued":{"date-parts":[["2008",3]]},"accessed":{"date-parts":[["2018",10,13]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>99%	<0.5	Full-scale fluidized bed[1]	Various	GAC / Acetic acid	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"gMjfE7DX","properties":{"formattedCitation":"(U.S. Department of Defense (U.S. DoD), 2009; Webster & Crowley, 2010, 2016; Webster & Litchfield, 2017)","plainCitation":"(U.S.

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					Department of Defense (U.S. DoD), 2009; Webster & Crowley, 2010, 2016; Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1081,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1081,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U. S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}},{"id":1019,"uris":["http://zotero.org/groups/945096/items/BI7SF8HW"],"uri":["http://zotero.org/groups/945096/items/BI7SF8HW"],"itemData":{"id":1019,"type":"speech","title":"Full-Scale Implementation of a Biological Fluidized Bed Drinking Water Treatment Plant for Nitrate and Perchlorate Treatment","publisher-place":"Ontario, CA","event":"2010 Water Education Foundation Water Quality and Regulatory Conference","event-place":"Ontario, CA","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2010",11,3]]}}},{"id":1018,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/g

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					roups/945096/items/BI5LYMZP"],"itemData":{"id":1018,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":1012,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":1012,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>99%	<5	Bench-scale fluidized bed	Nitrate, metals, volatile organics	GAC / Acetic acid	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"BWN3iGiU","properties":{"formattedCitation":"(Polk et al., 2001)","plainCitation":"(Polk et al., 2001)","noteIndex":0},"citationItems":[{"id":1106,"uris":["http://zotero.org/groups/945096/items/82QHFD5E"],"uri":["http://zotero.org/groups/945096/items/82QHFD5E"],"itemData":{"id":1106,"type":"speech","title":"Case Study of Ex-Situ Biological Treatment of Perchlorate-Contaminated Groundwater","publisher-place":"San Diego, CA","event":"4th Tri-Services

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					Environmental Technology Symposium","event-place":"San Diego, CA","author":[{"family":"Polk","given":"J."},{"family":"Murray","given":"C."},{"family":"Onewokae","given":"D.E."},{"family":"Tolbert","given":"D.E."},{"family":"Togna","given":"A.P."},{"family":"Guarini","given":"W.J."},{"family":"Frisch","given":"S."},{"family":"Del Vecchio","given":"M."}],"issued":{"date-parts":[["2001",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>99%	220 to 280	Bench-scale fluidized bed	Nitrate (15.4), sulfate (12.5)	GAC / Acetate or proprietary glycerol solution	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"sfS1st9B","properties":{"formattedCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016)","plainCitation":"(Kotlarz, Upadhyaya, Togna, & Raskin, 2016)","noteIndex":0},"citationItems":[{"id":1132,"uris":["http://zotero.org/groups/945096/items/E5WRR4HD"],"uri":["http://zotero.org/groups/945096/items/E5WRR4HD"],"itemData":{"id":1132,"type":"article-journal","title":"Evaluation of electron donors for biological perchlorate removal highlights the importance of diverse perchlorate-reducing populations","container-title":"Environmental Science: Water Research & Technology","page":"1049-1063","volume":"2","author":[{"family":"Kotlarz","given":"N."},{"family":"Upadhyaya","given":"G."},{"family":"Togna","given":"P."},{"family":"Raskin","given":"L."}],"issued":{"date-parts":[["2016"]]}}}],"schema":"https://github.com/citation-style-

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					language/schema/raw/master/csl-citation.json"}]
>99%	350 to <4	Full-scale fluidized bed[2]	Nitrate (1.9), sulfate (300)	GAC / Acetic acid, ethanol	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"hRCwdIbm","properties":{"formattedCitation":"(Polk et al., 2001)","plainCitation":"(Polk et al., 2001)","noteIndex":0},"citationItems":[{"id":1106,"uris":["http://zotero.org/groups/945096/items/82QHFD5E"],"uri":["http://zotero.org/groups/945096/items/82QHFD5E"],"itemData":{"id":1106,"type":"speech","title":"Case Study of Ex-Situ Biological Treatment of Perchlorate-Contaminated Groundwater","publisher-place":"San Diego, CA","event":"4th Tri-Services Environmental Technology Symposium","event-place":"San Diego, CA","author":[{"family":"Polk","given":"J."},{"family":"Murray","given":"C."},{"family":"Onewokae","given":"D.E."},{"family":"Tolbert","given":"D.E."},{"family":"Togna","given":"A.P."},{"family":"Guarini","given":"W.J."},{"family":"Frisch","given":"S."},{"family":"Del Vecchio","given":"M."}],"issued":{"date-parts":[["2001",6]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>99%	<2	Bench-scale fluidized bed	Sulfate (5 to 10)	GAC, sand / Ethanol, methanol, or mix	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"qSwnvSu3","properties":{"formattedCitation":"(Greene & Pitre, 2000)","plainCitation":"(Greene & Pitre, 2000)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1146,"uris":["http://zotero.org/groups/945096/items/LS46AD5H"],"uri":["http://zotero.o

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					rg/groups/945096/items/LS46AD5H"],"itemData":{"id":1146,"type":"chapter","title":"Treatment of Groundwater Containing Perchlorate using Biological Fluidized Bed Reactors with GAC or Sand Media","container-title":"Perchlorate in the Environment","publisher":"Kluwer Academic/Plenum","publisher-place":"New York, NY","event-place":"New York, NY","author":[{"family":"Greene","given":"M.R."},{"family":"Pitre","given":"M.P."}],"editor":[{"family":"Urbansky","given":"E.T."}],"issued":{"date-parts":[["2000"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>99%	<4	Full-scale fluidized bed[3]	Not reported	GAC / Ethanol	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"sAW1jo38","properties":{"formattedCitation":"(Greene & Pitre, 2000)","plainCitation":"(Greene & Pitre, 2000)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1146,"uris":["http://zotero.org/groups/945096/items/LS46AD5H"],"uri":["http://zotero.org/groups/945096/items/LS46AD5H"],"itemData":{"id":1146,"type":"chapter","title":"Treatment of Groundwater Containing Perchlorate using Biological Fluidized Bed Reactors with GAC or Sand Media","container-title":"Perchlorate in the Environment","publisher":"Kluwer Academic/Plenum","publisher-place":"New York, NY","event-place":"New York, NY","author":[{"family":"Gree

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					ne","given":"M.R."},{"family":"Pitre","given":"M.P."}],"editor":[{"family":"Urbansky","given":"E.T."}],"issued":{"date-parts":[["2000"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
>97%	<6	Bench-scale fluidized bed	Nitrate (13), sulfate (9.3 to 16.8)	GAC / Acetic acid or proprietary carbohydrate solution	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"yEumWcAd","properties":{"formattedCitation":"(Upadhyaya, Kotlarz, Togna, & Raskin, 2015)","plainCitation":"(Upadhyaya, Kotlarz, Togna, & Raskin, 2015)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1071,"uris":["http://zotero.org/groups/945096/items/KLWCLIE4"],"uri":["http://zotero.org/groups/945096/items/KLWCLIE4"],"itemData":{"id":1071,"type":"article-journal","title":"Carbohydrate-Based Electron Donor for Biological Nitrate and Perchlorate Removal From Drinking Water","container-title":"Journal - American Water Works Association","page":"E674-E684","volume":"107","issue":"12","source":"Wiley Online Library","abstract":"This study evaluated the feasibility of replacing acetic acid with a commercial carbohydrate-based electron donor (CBED) for removal of nitrate and perchlorate (ClO4–) from drinking water. Bench-scale biologically active carbon fixed-bed and fluidized-bed reactors (FXBR and FLBR, respectively), with an initial empty bed contact time (EBCT) of 42.8 min, were fed simulated groundwater containing 15 mg/L nitrate as nitrogen and 200 µg/L ClO4–

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					. EBCT in the FLBR after final expansion was 80.5 min. During the first 100 days using acetic acid at 125 mg/L chemical oxygen demand (COD), complete nitrate removal was achieved in both systems, whereas perchlorate in the FXBR and FLBR effluents remained below 3 and 6 µg/L ClO4–, respectively. For comparable removals, influent COD requirement was higher with the CBED. Biomass yields with acetic acid and the CBED were 0.54–0.58 and 0.59–0.74 mg CODbiomass/mg CODsubstrate, respectively. The higher yield with the CBED resulted in more frequent maintenance requirements.","DOI":"10.5942/jawwa.2015.107.0143","ISSN":"1551-8833","language":"en","author":[{"family":"Upadhyaya","given":"Giridhar"},{"family":"Kotlarz","given":"Nadine"},{"family":"Togna","given":"Paul"},{"family":"Raskin","given":"Lutgarde"}],"issued":{"date-parts":[["2015",12,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]
92 to 98%	<4	Field-scale fluidized bed[5]	Various	GAC / Ethanol	[ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"nj3wXeRQ","properties":{"formattedCitation":"(Gilbert, Clark, Kavanaugh, McCarty, & Trussell, 2001; Harding Engineering and Environmental Services (ESE), 2001)","plainCitation":"(Gilbert, Clark, Kavanaugh, McCarty, & Trussell, 2001; Harding Engineering and Environmental Services (ESE),

Removal Efficiency	Resulting Concentration (µg/L)	Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
					2001)","noteIndex":0},"citationItems":[{"id":1149,"uris":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"uri":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"itemData":{"id":1149,"type":"report","title":"Review of Phase 2 Treatibility Study: Aerojet Facility, Rancho Cordova, California","collection-title":"Expert Panel Final Report prepared for Aerojet","author":[{"family":"Gilbert","given":"J.B."},{"family":"Clark","given":"R."},{"family":"Kavanaugh","given":"M."},{"family":"McCarty","given":"P."},{"family":"Trussell","given":"R.R."}],"issued":{"date-parts":[["2001"]]}}},{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]

Notes:
1. Rialto Well #2 site in Rialto, California
2. Longhorn Army Ammunition Plant in Karnak, Texas
3. Aerojet facility in Rancho Cordova, California
4. Six-month field test in Santa Clarita, California
5. Eight-month field test in Rancho Cordova, California, supplying water for potable use

3.1.2 Are the effects of water quality parameters on treatment effectiveness and reliability well-known?

Yes. As shown in [REF _Ref297622741 \h * MERGEFORMAT], biological treatment remains effective even in the presence of certain co-occurring contaminants. Nitrate and sulfate were present in nearly all of the studies and did not appear to interfere with the removal efficiency of the process. Biological treatment also has been shown effective in the presence of metals, volatile organic compounds, and other contaminants including N-nitrosodimethlamine and 1,4-dioxane [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"LkCeiwr9","properties":{"formattedCitation":"(Harding Engineering and Environmental Services (ESE), 2001; Polk et al., 2001; U.S. Department of Defense (U.S. DoD), 2000)","plainCitation":"(Harding Engineering and Environmental Services (ESE), 2001; Polk et al., 2001; U.S. Department of Defense (U.S. DoD), 2000)","noteIndex":0},"citationItems":[{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1106,"uris":["http://zotero.org/groups/945096/items/82QHFD5E"],"uri":["http://zotero.org/groups/945096/items/82QHFD5E"],"itemData":{"id":1106,"type":"speech","title":"Case Study of Ex-Situ Biological Treatment of Perchlorate-Contaminated Groundwater","publisher-place":"San Diego, CA","event":"4th Tri-Services Environmental Technology Symposium","event-place":"San Diego, CA","author":[{"family":"Polk","given":"J."},{"family":"Murray","given":"C."},{"family":"Onewokae","given":"D.E."},{"family":"Tolbert","given":"D.E."},{"family":"Togna","given":"A.P."},{"family":"Guarini","given":"W.J."},{"family":"Frisch","given":"S."},{"family":"Del Vecchio","given":"M."}],"issued":{"date-parts":[["2001",6]]}}},{"id":1078,"uris":["http://zotero.org/groups/945096/items/U99PPGIM"],"uri":["http://zotero.org/groups/945096/items/U99PPGIM"],"itemData":{"id":1078,"type":"report","title":"Ammonium Perchlorate Biodegradation for Industrial Wastewater Treatment","collection-title":"ESTCP Cost and Performance Report","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2000"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Nevertheless, raw water quality plays a role in the design of a biological treatment system. In identifying design criteria for use in full-scale treatment plant designs, the Harding ESE [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"zlIiHyxF","properties":{"formattedCitation":"(2001)","plainCitation":"(2001)","noteIndex":0},"citationItems":[{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services

(ESE)","given":""}],"issued":{"date-parts":[["2001"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] authors included expected raw water dissolved oxygen, nitrate, perchlorate, and total phosphorous concentrations as necessary considerations, along with water temperature. In particular, temperature plays an important role in determining the rate of biomass growth. Electron donor dose requirements increase with decreasing temperature. At temperatures below 10 degrees C, biomass growth is inhibited and bioremediation becomes unfeasible [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"pNAKxFcY","properties":{"formattedCitation":"(Dugan, 2010a, 2010b; Dugan et al., 2009)","plainCitation":"(Dugan, 2010a, 2010b; Dugan et al., 2009)","noteIndex":0},"citationItems":[{"id":1159,"uris":["http://zotero.org/groups/945096/items/IIXUW45F"],"uri":["http://zotero.org/groups/945096/items/IIXUW45F"],"itemData":{"id":1159,"type":"article","title":"Supporting data for presentation: The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1160,"uris":["http://zotero.org/groups/945096/items/X3WWHCXS"],"uri":["http://zotero.org/groups/945096/items/X3WWHCXS"],"itemData":{"id":1160,"type":"speech","title":"The Impact of Temperature on Biological Perchlorate Removal and Downstream Effluent Polishing","publisher-place":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","event-place":"U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory","author":[{"family":"Dugan","given":"N.R."}],"issued":{"date-parts":[["2010",12,8]]}}},{"id":1158,"uris":["http://zotero.org/groups/945096/items/FLVLSXCS"],"uri":["http://zotero.org/groups/945096/items/FLVLSXCS"],"itemData":{"id":1158,"type":"speech","title":"The Impact of Temperature on Anaerobic Biological Perchlorate Treatment","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dugan","given":"N.R."},{"family":"Williams","given":"D.J."},{"family":"Meyer","given":"M."},{"family":"Schneider","given":"R.R."},{"family":"Speth","given":"T.F."},{"family":"Metz","given":"D.H."}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

3.1.3 Is the technology reliable enough to continuously meet a drinking water MCL?

Continuous destruction of perchlorate in a biological treatment system depends heavily on influent water temperature (see above under Question [REF _Ref525292787 \r \h]). Thus, systems with seasonal variation in water temperature such that temperature drops below 10 degrees C in the winter months would not be able to rely on biological treatment year-round. Systems with a constant water temperature or one that remains warm enough year-round, on the other hand, should be able to continuously meet an MCL.

3.1.4 Is additional research needed?

No. Additional research is not required.

3.2 History of Full-Scale Operation for Biological Treatment

3.2.1 Do existing studies include full-scale operations at drinking water treatment facilities?

Yes. Although most of the full-scale systems are part of perchlorate remediation projects in which treated water is not used as drinking water, fluidized bed operations supplying drinking water do exist. For example, one remediation facility conducted an eight-month fluidized bed field test that supplied potable water to local water companies [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"S3DYMP8P","properties":{"formattedCitation":"(Gilbert et al., 2001; Harding Engineering and Environmental Services (ESE), 2001)","plainCitation":"(Gilbert et al., 2001; Harding Engineering and Environmental Services (ESE), 2001)","noteIndex":0},"citationItems":[{"id":1149,"uris":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"uri":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"itemData":{"id":1149,"type":"report","title":"Review of Phase 2 Treatibility Study: Aerojet Facility, Rancho Cordova, California","collection-title":"Expert Panel Final Report prepared for Aerojet","author":[{"family":"Gilbert","given":"J.B."},{"family":"Clark","given":"R."},{"family":"Kavanaugh","given":"M."},{"family":"McCarty","given":"P."},{"family":"Trussell","given":"R.R."}],"issued":{"date-parts":[["2001"]]}}},{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Furthermore, the success of several demonstration studies led to the design and installation of a full-scale fluidized bed system supplying drinking water to the West Valley Water District and the City of Rialto. This system completed construction in 2013 and the system underwent extensive testing before receiving its operating permit and beginning to produce drinking water in 2016 [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"gw7638Au","properties":{"formattedCitation":"(Webster & Crowley, 2010, 2016; Webster & Litchfield, 2017)","plainCitation":"(Webster & Crowley, 2010, 2016; Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1019,"uris":["http://zotero.org/groups/945096/items/BI7SF8HW"],"uri":["http://zotero.org/groups/945096/items/BI7SF8HW"],"itemData":{"id":1019,"type":"speech","title":"Full-Scale Implementation of a Biological Fluidized Bed Drinking Water Treatment Plant for Nitrate and Perchlorate Treatment","publisher-place":"Ontario, CA","event":"2010 Water Education Foundation Water Quality and Regulatory Conference","event-place":"Ontario, CA","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2010",11,3]]}}},{"id":1018,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":1018,"type":"sp

eech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and
Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-
parts":[["2016",6,21]]}},{"id":1012,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":1012,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-
parts":[["2017"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

3.2.2 Are there studies of full-scale treatment of residuals that fully characterize residual waste streams and disposal options?

Yes. Because biological treatment offers complete destruction of the perchlorate ion, the technology does not generate a perchlorate-bearing waste stream. An active bioreactor, however, will have a continuous growth of biomass. Assuming the addition of a sufficient amount of electron donor substrate, the quantity of biomass generated will depend on the concentrations of dissolved oxygen, nitrate, and perchlorate available for consumption. In most bioreactor designs, excess biomass must be removed periodically, which results in one or more residual streams.

In fixed bed bioreactors, biomass removal typically is accomplished using a backwash process, which generates spent backwash water containing the excess biosolids (and some lost media). This backwash water is non-toxic and can typically be discharged to a local sewer [ADDIN ZOTERO_ITEM CSL_CITATION
{"citationID":"3FB0USxA","properties":{"formattedCitation":"(U.S. Department of Defense (U.S. DoD), 2008a)","plainCitation":"(U.S. Department of Defense (U.S. DoD), 2008a)","noteIndex":0},"citationItems":[{"id":1074,"uris":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"uri":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"itemData":{"id":1074,"type":"report","title":"Direct Fixed-bed Biological Perchlorate Destruction Demonstration","genre":"ESTCP Final Report (ER-0544)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-
parts":[["2008",9,25]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. For facilities without the option of sewer disposal, a clarification and recycle process would be needed.

For fluidized bed reactors, one case study describes the use of a continuously operated separation device that uses supplied air to remove media and biomass from the top of the bed and direct it to a separation chamber. This arrangement was used in combination with an in-bed eductor to intermittently remove biomass growth from deeper within the bed. After treatment through an adsorption clarifier and multimedia filter, the study reports that the remaining residuals were "dilute enough that no special handling or pretreatment requirements should be necessary for most/all POTWs to accept" [ADDIN ZOTERO_ITEM CSL_CITATION
{"citationID":"Frf46rxD","properties":{"formattedCitation":"(U.S. Department of Defense (U.S. DoD), 2009)","plainCitation":"(U.S. Department of Defense (U.S. DoD),

2009)","noteIndex":0},"citationItems":[{"id":1081,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1081,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Downstream polishing through filtration, when used as post-treatment (see Question [REF _Ref525293735 \r \h]), can also generate residual wastes in the form of backwash water and separated solids. The authors of the Harding ESE [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Mbll2ueB","properties":{"formattedCitation":"(2001)","plainCitation":"(2001)","noteIndex":0},"citationItems":[{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] report suggest that clarifier solids could be discharged directly to sewer or filter pressed to reduce volume prior to ultimate disposal. The full-scale drinking water treatment facility in Rialto uses dissolved air floatation, followed by a sludge press, to treat backwash from post-treatment filtration [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"5Mxr8mDs","properties":{"formattedCitation":"(Webster & Litchfield, 2017)","plainCitation":"(Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1012,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":1012,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Backwash water from downstream polishing would be expected to have characteristics similar to water from direct backwash of a fixed bed reactor.

3.2.3 Can the bench or pilot studies be scaled up to represent full-scale treatment, including residuals generation and handling?

Yes. Given the experience with full-scale remediation projects, the bench studies, pilot studies, and temporary field tests generally provide sufficient data to represent full-scale drinking water treatment.

3.2.4 Is additional research needed?

No. Additional research is not required.

3.3 General Geographic Applicability for Biological Treatment

3.3.1 What regions do the existing research areas represent?

The studies of biological treatment of perchlorate have been conducted in California and Texas.

3.3.2 Is it known that regional water quality variations will limit treatment effectiveness or reliability in some areas?

As discussed above (see Question [REF _Ref525292787 \r \h]), water temperature is a critical variable in the ability of biological treatment to continuously destroy perchlorate. Regions not studied may be more likely than California and Texas to have cold water and/or seasonally variable water temperature. Because the effect of temperature is well understood, however, it should be feasible to determine whether biological treatment will be effective for a given system based on a water temperature record.

In addition to external electron donors, bacteria in bioreactors require macro- and micro-nutrients in order to grow and effectively reduce perchlorate. Thus, concentrations of these nutrients in the raw water are a consideration in bioreactor effectiveness. Macro-nutrients include phosphorous and nitrogen, and necessary micro-nutrients include sulfur and iron. While source water typically contains sufficient micro-nutrients, it sometimes has insufficient amounts of phosphorous and nitrogen to allow for bacterial growth. As a result, some full-scale designs have required supplemental addition of one or both of these nutrients [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"NDoHjLOr","properties":{"formattedCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","plainCitation":"(Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a, 2009)","noteIndex":0},"citationItems":[{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1074,"uris":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"uri":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"itemData":{"id":1074,"type":"report","title":"Direct Fixed-bed Biological Perchlorate Destruction Demonstration","genre":"ESTCP Final Report (ER-0544)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008",9,25]]}}},{"id":1081,"uris":["http://zotero.org/groups/945096/items/9FHLVTXY"],"uri":["http://zotero.org/groups/945096/items/9FHLVTXY"],"itemData":{"id":1081,"type":"report","title":"Demonstration of a Full-Scale Fluidized Bed Bioreactor for the Treatment of Perchlorate at Low Concentrations in Groundwater","genre":"Environmental Security Technology Certification Program (ESTCP) Final Report (ER-0543)","author":[{"family":"U.S. Department of Defense (U.S. DoD)","given":""}],"issued":{"date-parts":[["2009"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

3.3.3 Are there any regional issues with respect to residuals handling or water resource use?

No. Regional residual handling and water resource needs are not expected to affect technology feasibility.

3.3.4 Is additional research needed?

No. Additional research is not required.

3.4 Compatibility of Biological Treatment with Other Treatment Processes

3.4.1 Have the effects (adverse or beneficial) of the treatment process on other processes likely to be present at existing plants been evaluated?

Yes. Biological treatment results in the production of soluble microbial organic products that become part of the treated water. The additional microorganisms increase disinfection demand for the downstream treatment processes. The biological treatment process also depletes the levels of oxygen in the treated water and can add turbidity and sulfides, which can have adverse effects on downstream treatment processes if not managed through post-treatment. Beneficial effects of biological treatment, on the other hand, include the potential to remove nitrate and disinfection byproduct precursors.

3.4.2 Will additional pre- or post-treatment be required for integration into an existing (or planned) treatment train?

Yes. Post-treatment will be needed to control the effects on other treatment processes (and also on the distribution system; see Question [REF _Ref525293735 \r \h]). In the field study of biological treatment for potable water [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2lg17wWj","properties":{"formattedCitation":"(Gilbert et al., 2001; Harding Engineering and Environmental Services (ESE), 2001)","plainCitation":"(Gilbert et al., 2001; Harding Engineering and Environmental Services (ESE), 2001)","noteIndex":0},"citationItems":[{"id":1149,"uris":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"uri":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"itemData":{"id":1149,"type":"report","title":"Review of Phase 2 Treatibility Study: Aerojet Facility, Rancho Cordova, California","collection-title":"Expert Panel Final Report prepared for Aerojet","author":[{"family":"Gilbert","given":"J.B."},{"family":"Clark","given":"R."},{"family":"Kavanaugh","given":"M."},{"family":"McCarty","given":"P."},{"family":"Trussell","given":"R.R."}],"issued":{"date-parts":[["2001"]]}}},{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], biological treatment was part of a train of seven different unit processes. The train included an aerator and multimedia filter serving as

post-treatment for the biological treatment step. Post-treatment was then followed by downstream processes to address other contaminants and water quality concerns. The downstream processes were an air stripper, advanced oxidation, granular activated carbon, and disinfection. Investigators concluded that each of the downstream treatment processes met desired removal efficiencies in a reliable manner [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"8ZXO6T2U","properties":{"formattedCitation":"(Gilbert et al., 2001)","plainCitation":"(Gilbert et al., 2001)","noteIndex":0},"citationItems":[{"id":1149,"uris":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"uri":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"itemData":{"id":1149,"type":"report","title":"Review of Phase 2 Treatibility Study: Aerojet Facility, Rancho Cordova, California","collection-title":"Expert Panel Final Report prepared for Aerojet","author":[{"family":"Gilbert","given":"J.B."},{"family":"Clark","given":"R."},{"family":"Kavanaugh","given":"M."},{"family":"McCarty","given":"P."},{"family":"Trussell","given":"R.R."}],"issued":{"date-parts":[["2001"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Thus, post-treatment appears able to manage the potential impacts of biological treatment on common downstream treatment processes.

3.4.3 Is additional research needed?

No. Additional research is not required.

3.5 Ability of Biological Treatment to Bring all of the Water System into Compliance

3.5.1 Will the treatment process adversely affect the distribution system or water resource decisions?

Yes, although distribution system impacts might be managed by post-treatment processes. As discussed under Question [REF _Ref525293762 \r \h], biological treatment adds microorganisms, depletes oxygen, and can add turbidity and sulfides. Therefore, post-treatment will typically be required for production of drinking water. Typical post-treatment processes include [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"s298IrQb","properties":{"formattedCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a; Webster & Crowley, 2016; Webster & Litchfield, 2017)","plainCitation":"(Dordelmann, 2009; Harding Engineering and Environmental Services (ESE), 2001; U.S. Department of Defense (U.S. DoD), 2008a; Webster & Crowley, 2016; Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1164,"uris":["http://zotero.org/groups/945096/items/Z7PC3BME"],"uri":["http://zotero.org/groups/945096/items/Z7PC3BME"],"itemData":{"id":1164,"type":"speech","title":"Full-Scale Biological Denitrification Plants in Germany, Austria and Poland","publisher-place":"Seattle, WA","event":"2009 AWWA Water Quality Technology Conference & Exposition","event-place":"Seattle, WA","author":[{"family":"Dordelmann","given":"O."}],"issued":{"date-parts":[["2009",11]]}}},{"id":1139,"uris":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"uri":["http://zotero.org/groups/945096/items/ZPGXUZPL"],"itemData":{"id":1139,"type":"report","title":"Final: Phase 2 Treatibility Study Report, Aerojet GET E/F Treatment Facility, Sacramento, California","collection-title":"Prepared for U.S. Environmental Protection Agency Region IX and Baldwin Park Operable Unit Cooperating Respondents, San Gabriel

Basin,California","author":[{"family":"Harding Engineering and Environmental Services (ESE)","given":""}],"issued":{"date-parts":[["2001"]]}}},{"id":1074,"uris":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"uri":["http://zotero.org/groups/945096/items/2ZCNIFHT"],"itemData":{"id":1074,"type":"report","title":"Direct Fixed-bed Biological Perchlorate Destruction Demonstration","genre":"ESTCP Final Report (ER-0544)","author":[{"literal":"U.S. Department of Defense (U.S. DoD)"}],"issued":{"date-parts":[["2008",9,25]]}}},{"id":1018,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":1018,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":1012,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":1012,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]:

- reoxygenation or aeration for saturation with oxygen, using hydrogen peroxide addition or an aeration tank
- a polishing filter (using GAC or mixed media) for removal of turbidity, sulfide, and/or dissolved organic content, possibly including coagulant addition before filtration
- disinfection via ultraviolet light or chlorination.

For the full-scale system supplying drinking water, the permit requirements also include instrumentation and controls (chlorine, pH, nitrate, sulfide, total organic carbon, and turbidity) to monitor performance [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"X2B7SNPa","properties":{"formattedCitation":"(Webster & Crowley, 2016; Webster & Litchfield, 2017)","plainCitation":"(Webster & Crowley, 2016; Webster & Litchfield, 2017)","noteIndex":0},"citationItems":[{"id":1018,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":1018,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":1012,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":1012,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

In the field study of biological treatment for potable water, which included the post-treatment processes listed above, investigators concluded that bacterial re-growth in the water distribution system would not be significant [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"eBy7BuRM","properties":{"formattedCitation":"(Gilbert et al., 2001)","plainCitation":"(Gilbert et al., 2001)","noteIndex":0},"citationItems":[{"id":1149,"uris":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"uri":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"itemData":{"id":1149,"type":"report","title":"Review of Phase 2 Treatibility Study: Aerojet Facility, Rancho Cordova, California","collection-title":"Expert Panel Final Report prepared for Aerojet","author":[{"family":"Gilbert","given":"J.B."},{"family":"Clark","given":"R."},{"family":"Kavanaugh","given":"M."},{"family":"McCarty","given":"P."},{"family":"Trussell","given":"R.R."}],"issued":{"date-parts":[["2001"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. They did not, however, address the potential for other distribution systems impacts.

3.5.2 Might the treatment process, residuals handling, or pre- or post-treatment requirements raise new environmental quality concerns?

Yes. Any of the impacts discussed above under Questions [REF _Ref525293762 \r \h] and [REF _Ref525293735 \r \h], if not adequately managed through post-treatment, could create new environmental quality concerns.

3.5.3 Is additional research needed?

Although Gilbert et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"olfre7L8","properties":{"formattedCitation":"(2001)","plainCitation":"(2001)","noteIndex":0},"citationItems":[{"id":1149,"uris":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"uri":["http://zotero.org/groups/945096/items/NHNGXTZ8"],"itemData":{"id":1149,"type":"report","title":"Review of Phase 2 Treatibility Study: Aerojet Facility, Rancho Cordova, California","collection-title":"Expert Panel Final Report prepared for Aerojet","author":[{"family":"Gilbert","given":"J.B."},{"family":"Clark","given":"R."},{"family":"Kavanaugh","given":"M."},{"family":"McCarty","given":"P."},{"family":"Trussell","given":"R.R."}],"issued":{"date-parts":[["2001"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] concluded that bacterial re-growth in the water distribution system would not be significant after post-treatment, additional research might be needed on the effectiveness of post-treatment processes in mitigating other distribution system impacts.

3.6 Reasonable Cost Basis for Biological Treatment for Large and Medium Systems

3.6.1 Is the technology currently used by medium and large systems (including uses for other treatment purposes)?

Yes. The full-scale system suppling drinking water was initially designed to treat 3 million gallons per day (MGD), with an ultimate capacity of 6 MGD so that water from additional wells might be treated in the future [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"VIVeF6LF","properties":{"formattedCitation":"(Webster & Crowley, 2016; Webster & Litchfield, 2017)","plainCitation":"(Webster & Crowley, 2016; Webster & Litchfield,

2017)","noteIndex":0},"citationItems":[{"id":1018,"uris":["http://zotero.org/groups/945096/items/BI5LYMZP"],"uri":["http://zotero.org/groups/945096/items/BI5LYMZP"],"itemData":{"id":1018,"type":"speech","title":"Biological treatment of perchlorate in groundwater.","event":"AWWA Annual Conference and Exposition","author":[{"family":"Webster","given":"T.D."},{"family":"Crowley","given":"T.J."}],"issued":{"date-parts":[["2016",6,21]]}}},{"id":1012,"uris":["http://zotero.org/groups/945096/items/64HZKA2M"],"uri":["http://zotero.org/groups/945096/items/64HZKA2M"],"itemData":{"id":1012,"type":"article-journal","title":"Full-scale biological treatment of nitrate and perchlorate for potable water production","container-title":"Journal AWWA","page":"30-40","volume":"109","issue":"5","author":[{"family":"Webster","given":"T.D."},{"family":"Litchfield","given":"M.H."}],"issued":{"date-parts":[["2017"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Fluidized bed reactors also have been used in remedial applications with design flows up to 10 MGD [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"sGC6KL1a","properties":{"formattedCitation":"(Greene & Pitre, 2000)","plainCitation":"(Greene & Pitre, 2000)","noteIndex":0},"citationItems":[{"id":1146,"uris":["http://zotero.org/groups/945096/items/LS46AD5H"],"uri":["http://zotero.org/groups/945096/items/LS46AD5H"],"itemData":{"id":1146,"type":"chapter","title":"Treatment of Groundwater Containing Perchlorate using Biological Fluidized Bed Reactors with GAC or Sand Media","container-title":"Perchlorate in the Environment","publisher":"Kluwer Academic/Plenum","publisher-place":"New York, NY","event-place":"New York, NY","author":[{"family":"Greene","given":"M.R."},{"family":"Pitre","given":"M.P."}],"editor":[{"family":"Urbansky","given":"E.T."}],"issued":{"date-parts":[["2000"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. This application re-injects treated water into an underlying aquifer; water is not used for drinking water.

3.6.2 Do the treatment studies provide sufficient information on design assumptions to allow cost modeling?

Detailed data are available from the treatment studies for all of the relevant design parameters, including:

- Support media type
- EBCT
- Bed expansion (for fluidized bed reactors)
- Electron donor type and dosage
- Nutrient addition
- Backwash design (for fixed bed reactors)
- Recycle rate (for fluidized bed reactors).

3.6.3 Is additional research needed?

No. Additional research is not required.

4 Best Available Technology Evaluation for Reverse Osmosis

Membrane filtration processes physically remove perchlorate ions from drinking water. These processes separate a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at a pressure greater than the normal osmotic pressure. The membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane and are removed as concentrate, or reject. This technique does not destroy the perchlorate ion and, therefore, creates a subsequent need for disposal or treatment of perchlorate-contaminated waste (the concentrate).

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by electrostatic repulsion of ions from the charged membrane surface. Membrane filtration technologies evaluated for perchlorate treatment include RO, nanofiltration (NF), and ultrafiltration (UF). As discussed under Question [REF _Ref525557229 \r \h], bench studies of NF and UF membranes show significant variability in these membranes' ability to remove perchlorate, depending on other constituents of the source water. Therefore, RO is the membrane process most suited for evaluation as BAT for perchlorate.

4.1 High Removal Efficiency for Reverse Osmosis

4.1.1 Have high removal efficiencies that achieve potential MCLs been documented?

Yes. Pilot-scale treatability work at the Metropolitan Water District of Southern California showed that NF and RO membranes consistently removed greater than 80 percent of the perchlorate (up to 98 percent for RO and 92 percent for NF) depending on influent concentration [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"9aji4xxe","properties":{"formattedCitation":"(Liang, Scott, Palencia, & Bruno, 1998)","plainCitation":"(Liang, Scott, Palencia, & Bruno, 1998)","noteIndex":0},"citationItems":[{"id":1015,"uris":["http://zotero.org/groups/945096/items/IQVVPD73"],"uri":["http://zotero.org/groups/945096/items/IQVVPD73"],"itemData":{"id":1015,"type":"paper-conference","title":"Investigation of Treatment Options for Perchlorate Removal.","publisher":"La Verne, CA: Metropolitan Water District of Southern California","publisher-place":"San Diego, CA","event":"AWWA Water Quality Technology Conference","event-place":"San Diego, CA","author":[{"family":"Liang","given":"S."},{"family":"Scott","given":"K.N."},{"family":"Palencia","given":"L.S."},{"family":"Bruno","given":"J."}],"issued":{"date-parts":[["1998"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Recycling 50 percent of the reject had no effect on overall perchlorate rejection. [REF _Ref297714356 \h * MERGEFORMAT] summarizes effectiveness results for this pilot-scale work, along with results from additional, smaller scale bench studies.

Bench-scale studies show the effects of steric/size exclusion and electrostatic exclusion on perchlorate transport through membranes to varying degrees. RO, while removing perchlorate,

also removes most other salts, requires high operating pressures, and is prone to significant flux decline. Membrane processes that operate at lower pressures, such as NF or UF, may be effective for perchlorate removal through selectivity based on size and/or charge. However, bench studies show significant variability in these membranes' ability to remove perchlorate, depending on other constituents of the source water. One bench study modified commercial NF membranes using layer-by-layer surface deposition of polyelectrolytes. This study showed that the modified NF membranes could achieve perchlorate removal nearly equal to that of RO membranes. The study, however, did not examine the effect of differing source water quality on the membranes and research on the modified membranes does not yet appear to have progressed beyond the lab [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"RxMxvldJ","properties":{"formattedCitation":"(Sanyal, Sommerfeld, & Lee, 2015)","plainCitation":"(Sanyal, Sommerfeld, & Lee, 2015)","noteIndex":0},"citationItems":[{"id":1014,"uris":["http://zotero.org/groups/945096/items/VTUDRPDL"],"uri":["http://zotero.org/groups/945096/items/VTUDRPDL"],"itemData":{"id":1014,"type":"article-journal","title":"Design of ultrathin nanostructured polyelectrolyte-based membranes with higher perchlorate rejection and high permeability","container-title":"Separation and Purification Technology","volume":"145","issue":"113-119","author":[{"family":"Sanyal","given":"O."},{"family":"Sommerfeld","given":"A.N."},{"family":"Lee","given":"I."}],"issued":{"date-parts":[["2015"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}].

Exhibit [SEQ Exhibit * ARABIC]. Perchlorate Effectiveness Results for Membranes

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
RO and NF [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Jkd1SU74","properties":{"formattedCitation":"(Liang et al., 1998)","plainCitation":"(Liang et al., 1998)","noteIndex":0},"citationItems":[{"id":1015,"uris":["http://zotero.org/groups/945096/items/IQVVPD73"],"uri":["http://zotero.org/groups/945096/items/IQVVPD73"],"itemData":{"id":1015,"type":"paper-conference","title":"Investigation of Treatment Options for Perchlorate Removal.","publisher":"La Verne, CA: Metropolitan Water District of Southern California","publisher-	RO up to 98% NF up to 92%	20 to 2,000 µg/L (some trials used perchlorate-spiked source water)	Metropolitan Water District of Southern California, La Verne Treatment Plant, CA; Pretreated Colorado River Water	Pilot study (12 gpm)

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
place":"San Diego, CA","event":"AWWA Water Quality Technology Conference","event-place":"San Diego, CA","author":[{"family":"Liang","given":"S."},{"family":"Scott","given":"K. N."},{"family":"Palencia","given":"L.S."},{"family":"Bruno","given":"J."}],"issued":{"date-parts":[["1998"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]				
Surfactant modified UF [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"7Od8XAKN","properties":{"formattedCitation":"(Jaekyung Yoon et al., 2003)","plainCitation":"(Jaekyung Yoon et al., 2003)","noteIndex":0},"citationItems":[{"id":1085,"uris":["http://zotero.org/groups/945096/items/PF2DJFVN"],"uri":["http://zotero.org/groups/945096/items/PF2DJFVN"],"itemData":{"id":1085,"type":"article-journal","title":"Use of surfactant modified ultrafiltration for perchlorate (Cl(O)(4-)) removal","container-title":"Water Research","page":"2001-2012","volume":"37","issue":"9","source":"PubMed","abstract":"Determinations of perchlorate anion (ClO(4)(-)) transport and rejection were performed using a surfactant modified	Up to 80%	100 µg/L (perchlorate-spiked)	Synthetic water and a blend of Colorado River Water and State Project Water from the Metropolitan Water District, CA	Bench study (225 milliliters per minute)

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
ultrafiltration (UF) membrane. Perchlorate anion (at a concentration of 100 microg/L of ClO(4)(-), spiked with KClO(4)) was introduced to the membrane as a pure component, in binary mixtures with other salts, cationic and anionic surfactants, and at various ionic strength conditions (conductivity). Also, a natural source water was spiked with perchlorate in the presence of cationic and anionic surfactants and used to determine the effects of a complex mixture (including natural organic matter (NOM)) on the observed rejection. All filtration measurements were performed at approximately the same permeate flow rate in order to minimize artifacts from mass transfer at the membrane interface. The objective of this study was to modify a negatively charged UF membrane in terms of the fundamental mechanisms, steric/size exclusion and electrostatic exclusion and to enhance perchlorate rejection, with synthetic water and a blend of Colorado River water and State Project water (CRW/SPW). Previous work suggested that perchlorate was dominantly rejected by electrostatic exclusion for charged				

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
nanofiltration (NF) and UF membranes (Rejection of perchlorate by reverse osmosis, nanofiltration and ultrafiltration (UF) membranes: mechanism and modeling. Ph.D. dissertation, University of Colorado, Boulder, USA, 2001). In that research, perchlorate rejection capability was quickly lost in the presence of a sufficient amount of other ions. However, this study showed that ClO(4)(-) was excluded from a (negatively) charged UF membrane with pores large with respect to the size of the ion. Although perchlorate rejection capability due to apparent electrostatic force was reduced in the presence of a cationic surfactant, a desired amount of the ClO(4)(-) was excluded by steric exclusion. The steric exclusion was due to decreasing membrane pore size caused by the adsorption of the cationic surfactant.","DOI":"10.1016/S0043-1354(02)00600-0","ISSN":"0043-1354","note":"PMID: 12691884","journalAbbreviation":"Water Res.","language":"eng", "author":[{"family":"Yoon","given":"Jaekyung"},{"family":"Yoon","given":"Yeomin"},{"family":"Amy","given":"Gary"},{"family":"Cho","given":"Jaeweon"},{"family":"Foss","giv				

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
en":"David"},{"family":"Kim","given":"Tae-Hyung"}],"issued":{"date-parts":[["2003",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]				
NF and UF [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"GRtQHCCe","properties":{"formattedCitation":"(Y. Yoon, Amy, Cho, Her, & Pellegrino, 2002)","plainCitation":"(Y. Yoon, Amy, Cho, Her, & Pellegrino, 2002)","noteIndex":0},"citationItems":[{"id":1087,"uris":["http://zotero.org/groups/945096/items/DGUADSQZ"],"uri":["http://zotero.org/groups/945096/items/DGUADSQZ"],"itemData":{"id":1087,"type":"article-journal","title":"Transport of perchlorate (ClO4−) through NF and UF membranes","container-title":"Desalination","page":"11-17","volume":"147","issue":"1","source":"Science Direct","abstract":"Measurements of the rejection of perchlorate anion (ClO4−) were performed using nanofiltration (NF) and ultrafiltration (UF) membranes. Aqueous solutions of perchlorate (at a concentration of 100 μg/L of ClO4− by “spiking” with KClO4) were fed to the membrane test apparatus. Solutions contained only	Up to 75%	100 μg/L (perchlorate-spiked)	Synthetic water with pure component perchlorate, also combined with other salts	Bench study (no flow given)

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
perchlorate, or an additional salt (KCl, K2SO4, or CaCl2) at overall ionic strengths of 30, 60, or 115 mS/cm, and pH adjusted to 4, 6, 8, or 10. The data were modeled by application of a non-equilibrium thermodynamic model. The model has five parameters: the molecular transport coefficient (ω), osmotic pressure gradient (ΔΠ), molecular reflection coefficient (σ), the average bulk fluid interfacial concentration between the feed and permeate side (Cavg), and the solvent flux (Jv). These parameters were determined by independent measurements (and calculation with minimum assumptions.) For example, the molecular transport coefficient (ω) was obtained by diffusion cell measurements under varying pH and conductivity conditions — generally it decreased with increasing pH and increased with conductivity for the membranes in our study. Measured and predicted perchlorate transport was in good agreement. Overall, the results indicate that, in a pure component system, target ions (in this case ClO4−) can be excluded from (negatively) charged membranes with pores large with respect to the				

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
size of the ion, but this rejection capability is quickly lost in the presence of a sufficient amount of other ions that can screen the apparent electrostatic force field. As intuitively expected, the perchlorate flux is governed by convection in large pore membranes.","DOI":"10.1016/S0011-9164(02)00564-7","ISSN":"0011-9164","journalAbbreviation":"Desalination","author":[{"family":"Yoon","given":"Yeomin"},{"family":"Amy","given":"Gary"},{"family":"Cho","given":"Jaeweon"},{"family":"Her","given":"Namguk"},{"family":"Pellegrino","given":"John"}],"issued":{"date-parts":[["2002",9,10]]}}}], "schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]				
NF and UF [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"j6jDrku0","properties":{"formattedCitation":"(Y. Yoon, Amy, Cho, & Pellegrino, 2005)","plainCitation":"(Y. Yoon, Amy, Cho, & Pellegrino, 2005)","noteIndex":0},"citationItems":[{"id":1086,"uris":["http://zotero.org/groups/945096/items/C6EW7ZPT"],"uri":["http://zotero.org/groups/945096/items/C6EW7ZPT"],"itemData":{"id":1086,"type":"article-journal","title":"Systematic Bench-Scale	NF up to 80% (natural water) or 89% (synthetic water) UF up to 5% (natural water) or 66% (synthetic water)	100 µg/L (perchlorate-spiked)	Synthetic water and Colorado River Water from the Metropolitan Water District, CA, spiked with perchlorate	Bench study (100 to 225 milliliters per minute)

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
Assessment of Perchlorate (ClO4 −) Rejection Mechanisms by Nanofiltration and Ultrafiltration Membranes","container-title":"Separation Science and Technology","page":"2105-2135","volume":"39","issue":"9","source":"Taylor and Francis+NEJM","abstract":"Measurements of the rejection of perchlorate anion (ClO4 −) have been performed by using two thin-film composite nanofiltration (NF) membranes and four ultrafiltration (UF) membranes. The latter four membranes are all from the same manufacturer and, ostensibly, from the same material family. These were chosen to systematically change the membranes steric properties, while keeping the same material chemistry, thus, the enthalpic interactions should stay constant. The perchlorate anion (at a concentration of 100 g/L of ClO4 − by “spiking” with KClO4) was presented to the membrane as a pure component, in binary mixtures with other salts, and at varying pH and ionic strength (conductivity). Also, a natural source water was “spiked” with perchlorate anion and used to document the effects of a complex mixture, including				

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
natural organic matter, on the observed rejection. All filtration measurements were performed at approximately the same permeate flow rate to minimize artifacts from mass transfer at the membrane interface. In general, the results indicate that, in a pure component system, target ions (in this case ClO4 −) can be significantly excluded from like-charged membranes with pores large with respect to the size of the ion, but this rejection capability decreases in the presence of a sufficient amount of other ions that can screen the electrostatic force field. #Contribution of the US Government, not subject to copyright in the United States","DOI":"10.1081/SS-120039304","ISSN":"0149-6395","author":[{"family":"Yoon","given":"Yeomin"},{"family":"Amy","given":"Gary"},{"family":"Cho","given":"Jaeweon"},{"family":"Pellegrino","given":"John"}],"issued":{"date-parts":[["2005",1,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]				
RO and NF [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"O5A7ZkCC","properties":{"formattedCitation":"(Nam et al.,	RO up to 95% NF up to 70%	100 µg/L (perchlorate-spiked)	Ground waters from the Castaic Lake Water Agency, CA	Bench study (no flow given)

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
2005)","plainCitation":"(Nam et al., 2005)","noteIndex":0},"c itationItems":[{"id":1113, "uris":["http://zotero.org/ groups/945096/items/Y HEV76YW"],"uri":["http:/ /zotero.org/groups/9450 96/items/YHEV76YW"], "itemData":{"id":1113,"ty pe":"paper- conference","title":"Perc hlorate Rejection by High-Pressure Membranes and Brine Stream Treatment by Chemical and Biological Processes.","publisher- place":"Phoenix, AZ","event":"American Water Works Association Membrane Technology Conference","event- place":"Phoenix, AZ","author":[{"family":" Nam","given":"S."},{"fam ily":"Kim","given":"S."},{" family":"Choi","given":"H ."},{"family":"Yoon","give n":""},{"family":"Silverste in","given":"J."},{"family" :"Amy","given":"G."}],"is sued":{"date- parts":[["2005"]]}}}],"sch ema":"https://github.co m/citation-style- language/schema/raw/ master/csl- citation.json"}]				
RO [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"4BC2CL2 B","properties":{"formatt edCitation":"(USEPA, 2005)","plainCitation":"(USEPA, 2005)","noteIndex":0},"c itationItems":[{"id":1046, "uris":["http://zotero.org/ groups/945096/items/E WAQ4GEK"],"uri":["http: //zotero.org/groups/945	From 125–2,000 µg/L to 5–80 µg/L	125 to 2,000 µg/L	Unspecified perchlorate-contaminated ground water	Bench study (no flow given)

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
096/items/EWAQ4GEK"],"itemData":{"id":1046," type":"article","title":"Perchlorate Treatment Technology Update: Federal Facilities Forum Issue Paper","publisher":"Office of Solid Waste and Emergency Response. EPA 542-R-05-015","author":[{"literal":" USEPA"}],"issued":{"date-parts":[["2005",5]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]				
RO and NF [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"v3oKqGrj", "properties":{"formatted Citation":"(J. Yoon, Yoon, Amy, & Her, 2005)","plainCitation":"(J. Yoon, Yoon, Amy, & Her, 2005)","noteIndex":0},"citationItems":[{"id":1011, "uris":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"uri":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"itemData":{"id":1011,"type":" article-journal","title":"Determination of perchlorate rejection and associated inorganic fouling (scaling) for reverse osmosis and nanofiltration membranes under various operating conditions","container-title":"Journal of Environmental Engineering","page":"726-733","author":[{"family":"	RO up to 95% NF up to 55%	100 µg/L (perchlorate-spiked)	Blend of Colorado River Water and State Project Water from the Metropolitan Water District, CA, spiked with perchlorate	Bench study (20 milliliters per minute)

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
Yoon","given":"J."},{"family":"Yoon","given":"Y."},{"family":"Amy","given":"G."},{"family":"Her","given":"N."}],"issued":{"date-parts":[["2005",5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]				
RO, NF, and UF [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"rf2SGryi","properties":{"formattedCitation":"(J. Yoon, Amy, & Yoon, 2005)","plainCitation":"(J. Yoon, Amy, & Yoon, 2005)","noteIndex":0},"citationItems":[{"id":1010,"uris":["http://zotero.org/groups/945096/items/HPHVBSWB"],"uri":["http://zotero.org/groups/945096/items/HPHVBSWB"],"itemData":{"id":1010,"type":"article-journal","title":"Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes.","container-title":"Water Science and Technology","page":"327-334","volume":"51","issue":"6-7","author":[{"family":"Yoon","given":"J."},{"family":"Amy","given":"G."},{"family":"Yoon","given":"Y."}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/	RO up to 95% NF up to 78% UF up to 29%	100 µg/L (perchlorate-spiked)	Synthetic water	Bench study (no flow given)

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
master/csl-citation.json"}]				
RO, NF, and surface modified NF [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Ta38LMgn","properties":{"formattedCitation":"(Sanyal et al., 2015)","plainCitation":"(Sanyal et al., 2015)","noteIndex":0},"citationItems":[{"id":1014,"uris":["http://zotero.org/groups/945096/items/VTUDRPDL"],"uri":["http://zotero.org/groups/945096/items/VTUDRPDL"],"itemData":{"id":1014,"type":"article-journal","title":"Design of ultrathin nanostructured polyelectrolyte-based membranes with higher perchlorate rejection and high permeability","container-title":"Separation and Purification Technology","volume":"145","issue":"113-119","author":[{"family":"Sanyal","given":"O."},{"family":"Sommerfeld","given":"A.N."},{"family":"Lee","given":"I."}],"issued":{"date-parts":[["2015"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]	RO up to 95.8% NF up to 70.1% Surface modified NF up to 93%	10,000 µg/L (perchlorate-spiked)	Perchlorate-spiked deionized water	Bench study (0.26 gpm)

4.1.2 Are the effects of water quality parameters on treatment effectiveness and reliability well-known?

Yes. In general, water quality affects the design (e.g., concentrate volume, cleaning frequency, antiscalant selection) of an RO system, but not removal efficiency. The literature specifically for perchlorate removal by membranes supports this conclusion. Higher variability in perchlorate removal with water quality has been found for NF and UF membranes than for RO membranes.

High levels of alkaline earth cations (Ca^{2+} or Mg^{2+}) can cause membrane scaling (Yoon et al., 2003), leading to a decline in product water flux. One study showed that calcium carbonate scaling was also associated with a decline in perchlorate rejection, likely because the scale reduced the surface charge of the membrane [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"OHeHUKrz","properties":{"formattedCitation":"(J. Yoon, Amy, et al., 2005)","plainCitation":"(J. Yoon, Amy, et al., 2005)","noteIndex":0},"citationItems":[{"id":1010,"uris":["http://zotero.org/groups/945096/items/HPHVBSWB"],"uri":["http://zotero.org/groups/945096/items/HPHVBSWB"],"itemData":{"id":1010,"type":"article-journal","title":"Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes.","container-title":"Water Science and Technology","page":"327-334","volume":"51","issue":"6-7","author":[{"family":"Yoon","given":"J."},{"family":"Amy","given":"G."},{"family":"Yoon","given":"Y."}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. Other substances, such as silica and microbial biomass, may also cause flux decline; however, there are no studies of the resulting effect on perchlorate rejection.

Membrane fouling can be reduced either by reducing the pH of the feed water or by adding an antiscalant chemical. However, for membranes that reject perchlorate electrostatically (primarily NF and UF membranes), studies of several synthetic waters show that a reduced feed pH reduces the rejection of perchlorate [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"wHL9VrcI","properties":{"formattedCitation":"(J. Yoon, Amy, et al., 2005; J. Yoon, Yoon, et al., 2005; Y. Yoon et al., 2005)","plainCitation":"(J. Yoon, Amy, et al., 2005; J. Yoon, Yoon, et al., 2005; Y. Yoon et al., 2005)","noteIndex":0},"citationItems":[{"id":1010,"uris":["http://zotero.org/groups/945096/items/HPHVBSWB"],"uri":["http://zotero.org/groups/945096/items/HPHVBSWB"],"itemData":{"id":1010,"type":"article-journal","title":"Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes.","container-title":"Water Science and Technology","page":"327-334","volume":"51","issue":"6-7","author":[{"family":"Yoon","given":"J."},{"family":"Amy","given":"G."},{"family":"Yoon","given":"Y."}],"issued":{"date-parts":[["2005"]]}}},{"id":1011,"uris":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"uri":["http://zotero.org/groups/945096/items/IIJW6E8Q"],"itemData":{"id":1011,"type":"article-journal","title":"Determination of perchlorate rejection and associated inorganic fouling (scaling) for reverse osmosis and nanofiltration membranes under various operating conditions","container-title":"Journal of Environmental Engineering","page":"726-733","author":[{"family":"Yoon","given":"J."},{"family":"Yoon","given":"Y."},{"family":"Amy","given":"G."},{"family":"Her","given":"N."}],"issued":{"date-parts":[["2005",5]]}}},{"id":1086,"uris":["http://zotero.org/groups/945096/items/C6EW7ZPT"],

"uri":["http://zotero.org/groups/945096/items/C6EW7ZPT"],"itemData":{"id":1086,"type":"article-journal","title":"Systematic Bench-Scale Assessment of Perchlorate (ClO4 −) Rejection Mechanisms by Nanofiltration and Ultrafiltration Membranes","container-title":"Separation Science and Technology","page":"2105-2135","volume":"39","issue":"9","source":"Taylor and Francis+NEJM","abstract":"Measurements of the rejection of perchlorate anion (ClO4 −) have been performed by using two thin-film composite nanofiltration (NF) membranes and four ultrafiltration (UF) membranes. The latter four membranes are all from the same manufacturer and, ostensibly, from the same material family. These were chosen to systematically change the membranes steric properties, while keeping the same material chemistry, thus, the enthalpic interactions should stay constant. The perchlorate anion (at a concentration of 100 g/L of ClO4 − by “spiking” with KClO4) was presented to the membrane as a pure component, in binary mixtures with other salts, and at varying pH and ionic strength (conductivity). Also, a natural source water was “spiked” with perchlorate anion and used to document the effects of a complex mixture, including natural organic matter, on the observed rejection. All filtration measurements were performed at approximately the same permeate flow rate to minimize artifacts from mass transfer at the membrane interface. In general, the results indicate that, in a pure component system, target ions (in this case ClO4 −) can be significantly excluded from like-charged membranes with pores large with respect to the size of the ion, but this rejection capability decreases in the presence of a sufficient amount of other ions that can screen the electrostatic force field. #Contribution of the US Government, not subject to copyright in the United States","DOI":"10.1081/SS-120039304","ISSN":"0149-6395","author":[{"family":"Yoon","given":"Yeomin"},{"family":"Amy","given":"Gary"},{"family":"Cho","given":"Jaeweon"},{"family":"Pellegrino","given":"John"}],"issued":{"date-parts":[["2005",1,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The lower pH has been shown to diminish the negative surface charge of the membranes, inhibiting the electrostatic rejection mechanism. One study [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"m52HhJol","properties":{"formattedCitation":"(J. Yoon, Amy, et al., 2005)","plainCitation":"(J. Yoon, Amy, et al., 2005)","noteIndex":0},"citationItems":[{"id":1010,"uris":["http://zotero.org/groups/945096/items/HPHVBSWB"],"uri":["http://zotero.org/groups/945096/items/HPHVBSWB"],"itemData":{"id":1010,"type":"article-journal","title":"Transport of target anions, chromate (Cr (VI)), arsenate (As (V)), and perchlorate (ClO4), through RO, NF, and UF membranes.","container-title":"Water Science and Technology","page":"327-334","volume":"51","issue":"6-7","author":[{"family":"Yoon","given":"J."},{"family":"Amy","given":"G."},{"family":"Yoon","given":"Y."}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] demonstrated that a phosphonate-based antiscalant improved both product water flux and perchlorate rejection. In these studies, perchlorate rejection by RO membranes was much less sensitive to the feed water pH.

The same studies demonstrated that a high concentration of other ions, particularly divalent cations, in the membrane feed water can reduce perchlorate rejection. Again, the studies attributed the reduced rejection to a diminished membrane surface charge. One study that included one natural water and several synthetic waters [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2RU601Fz","properties":{"formattedCitation":"(Y. Yoon et al., 2005)","plainCitation":"(Y. Yoon et al., 2005)","noteIndex":0},"citationItems":[{"id":1086,"uris":["http://zotero.org/groups/945096/item

s/C6EW7ZPT"],"uri":["http://zotero.org/groups/945096/items/C6EW7ZPT"],"itemData":{"id":1086,"type":"article-journal","title":"Systematic Bench-Scale Assessment of Perchlorate (ClO4 −) Rejection Mechanisms by Nanofiltration and Ultrafiltration Membranes","container-title":"Separation Science and Technology","page":"2105-2135","volume":"39","issue":"9","source":"Taylor and Francis+NEJM","abstract":"Measurements of the rejection of perchlorate anion (ClO4 −) have been performed by using two thin-film composite nanofiltration (NF) membranes and four ultrafiltration (UF) membranes. The latter four membranes are all from the same manufacturer and, ostensibly, from the same material family. These were chosen to systematically change the membranes steric properties, while keeping the same material chemistry, thus, the enthalpic interactions should stay constant. The perchlorate anion (at a concentration of 100 g/L of ClO4 − by “spiking” with KClO4) was presented to the membrane as a pure component, in binary mixtures with other salts, and at varying pH and ionic strength (conductivity). Also, a natural source water was “spiked” with perchlorate anion and used to document the effects of a complex mixture, including natural organic matter, on the observed rejection. All filtration measurements were performed at approximately the same permeate flow rate to minimize artifacts from mass transfer at the membrane interface. In general, the results indicate that, in a pure component system, target ions (in this case ClO4 −) can be significantly excluded from like-charged membranes with pores large with respect to the size of the ion, but this rejection capability decreases in the presence of a sufficient amount of other ions that can screen the electrostatic force field. #Contribution of the US Government, not subject to copyright in the United States","DOI":"10.1081/SS-120039304","ISSN":"0149-6395","author":[{"family":"Yoon","given":"Yeomin"},{"family":"Amy","given":"Gary"},{"family":"Cho","given":"Jaeweon"},{"family":"Pellegrino","given":"John"}],"issued":{"date-parts":[["2005",1,2]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] found that the natural water had worse perchlorate rejection than the most similar synthetic water for NF and UF membranes.

4.1.3 Is the technology reliable enough to continuously meet a drinking water MCL?

Yes. In general, RO is an established, reliable technology that has been used successfully to meet other MCLs. There is nothing unique about perchlorate removal by RO that suggests using it for this contaminant would reduce the technology’s reliability.

4.1.4 Is additional research needed?

No. Additional research is not required.

4.2 History of Full-Scale Operation for Reverse Osmosis

4.2.1 Do existing studies include full-scale operations at drinking water treatment facilities?

There are no known full-scale RO facilities specifically for the removal of perchlorate. There are, however, a large number of drinking water treatment facilities that use RO for other contaminants.

4.2.2 Are there studies of full-scale treatment of residuals that fully characterize residual waste streams and disposal options?

There are no known full-scale studies of residuals from RO facilities specifically for the removal of perchlorate. In general, however, the characteristics of RO residuals are predictable and handling and treatment options are well understood. RO produces a waste stream called the concentrate (or reject). This waste stream contains all removed dissolved solids. Membrane system designs generally set a recovery rate (i.e., the ratio of permeate to feed flow) based on the scaling potential of the feed water. The presence of a particular target contaminant has little or no effect on the selected recovery rate. Typical recovery rates are 70 to 85 percent, which means that concentrate flows can account for 15 to 30 percent of influent (i.e., 100 percent minus the recovery rate). There is nothing unique about perchlorate removal by RO that suggests recovery rates and concentrate flows would be different. Therefore, it is likely that the concentrate flow from a full-scale RO facility removing perchlorate would represent a substantial share of influent flows, implying a fairly large perchlorate-contaminated waste stream for subsequent treatment or disposal.

For disposal of RO residuals, the majority of systems use surface water discharge or discharge to sanitary sewer, with a small number using deep well injection, evaporation ponds, or spray irrigation [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"j91VNm1d","properties":{"formattedCitation":"(U.S. Department of Interior (DoI), 2001)","plainCitation":"(U.S. Department of Interior (DoI), 2001)","noteIndex":0},"citationItems":[{"id":1080,"uris":["http://zotero.org/groups/945096/items/42RS957X"],"uri":["http://zotero.org/groups/945096/items/42RS957X"],"itemData":{"id":1080,"type":"report","title":"Membrane Concentrate Disposal: Practices and Regulation","collection-title":"Desalination and Water Purification Research and Development Program Report No. 69","publisher":"Bureau of Reclamation, Technical Service Center, Water Treatment Engineering and Research Group","URL":"http://www.usbr.gov/pmts/water/media/pdfs/report069.pdf","author":[{"literal":"U.S. Department of Interior (DoI)"}],"issued":{"date-parts":[["2001",9]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. The large volume of residuals is a well-known obstacle to adoption of RO technology, in general. In the case of perchlorate removal by centralized treatment plants, the high perchlorate concentration in the residuals might limit the disposal options or require additional treatment prior to disposal, depending on state and local discharge regulations. Studies of treatment of perchlorate-bearing RO residuals are limited to a few laboratory-scale studies. These include biological [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"S96CtKCx","properties":{"formattedCitation":"(Giblin, Losi, Hosangadi, & Frankenberger, 2002)","plainCitation":"(Giblin, Losi, Hosangadi, & Frankenberger, 2002)","noteIndex":0},"citationItems":[{"id":1150,"uris":["http://zotero.org/groups/945096/items/QMU78XKX"],"uri":["http://zotero.org/groups/945096/items/QMU78XKX"],"itemData":{"id":1150,"type":"article-journal","title":"Bacterial Perchlorate Reduction in Simulated Reverse Osmosis Rejectate","container-title":"Bioremediation Journal","page":"105-112","volume":"6","issue":"2","author":[{"family":"Giblin","given":"T."},{"family":"Losi","given":"M.E."},{"family":"Hosangadi","given":"V."},{"family":"Frankenberger","given":"W.T."}],"issued":{"date-parts":[["2002"]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"}] and thermal treatment [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"H9rR7CX7","properties":{"formattedCitation":"(Applied Research Associates (ARA), 2000)","plainCitation":"(Applied Research Associates (ARA), 2000)","noteIndex":0},"citationItems":[{"id":995,"uris":["http://zotero.org/groups/945096/items/I87D72M4"],"uri":["http://zotero.org/groups/945096/items/I87D72M4"],"itemData":{"id":995,"type":"report","title":"Final Report: Hydrothermal/Thermal Decomposition of Perchlorate","publisher":"Investigators: L. Li, E.N. EPA Small Business Innovation Research, EPA Grant Number 68D99032","author":[{"literal":"Applied Research Associates (ARA)"}],"issued":{"date-parts":[["2000"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] of RO concentrate. Urbansky and Schock [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"dkrfUKm7","properties":{"formattedCitation":"(1999)","plainCitation":"(1999)","noteIndex":0},"citationItems":[{"id":1069,"uris":["http://zotero.org/groups/945096/items/K8JCZ3AL"],"uri":["http://zotero.org/groups/945096/items/K8JCZ3AL"],"itemData":{"id":1069,"type":"article-journal","title":"Issues in managing the risks associated with perchlorate in drinking water","container-title":"Journal of Environmental Management","page":"79-95","volume":"56","issue":"2","source":"ScienceDirect","abstract":"Perchlorate (ClO4−) contamination of ground and surface waters has placed drinking water supplies at risk in communities throughout the US, especially in the West. Several major assessment studies of that risk in terms of health and environmental impact are expected to be released by the US Environmental Protection Agency in early 1999, and preparations for how best to manage and minimize that risk are underway. Perchlorate salts are used in rocket and missile propulsion; therefore, it is believed that the pollution is derived primarily from defense and supporting industry. Due to the perchlorate anion's fundamental physical and chemical nature, the contamination is difficult to treat or remediate. The current work describes the evolution of the unique team-based governmental response to the problem and the rapidity of its development. Technologies under consideration that may prove feasible for treating contaminated water supplies are discussed and evaluated. The impact of these treatment technologies on other regulatory compliance matters and limitations of space, cost, and other resources are considered. Practical guidelines for approaching the problem are outlined, and current research needs are identified.","DOI":"10.1006/jema.1999.0274","ISSN":"0301-4797","journalAbbreviation":"Journal of Environmental Management","author":[{"family":"Urbansky","given":"E. T."},{"family":"Schock","given":"M. R."}],"issued":{"date-parts":[["1999",6,1]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] note, however, that membrane filtration point-of-use devices can be practical options for homeowners, or other small or remote users. Depending upon the permitted perchlorate discharge levels, the concentrate can often be disposed in the sanitary sewer system, where it will essentially recombine with the raw water in the sewage stream.

4.2.3 Can the bench or pilot studies be scaled up to represent full-scale treatment, including residuals generation and handling?

Yes. As a mature and established technology, the scale-up of RO, in general, from bench- to pilot- to full-scale is well understood.

4.2.4 Is additional research needed?

In general, additional research is not required. In cases where regional or system-specific conditions associated with perchlorate-bearing residuals management present a significant barrier, however, additional research on residuals treatment prior to disposal would be useful.

4.3 General Geographic Applicability for Reverse Osmosis

4.3.1 What regions do the existing research areas represent?

As shown in [REF _Ref297714356 \h * MERGEFORMAT], most of the existing pilot- and bench-scale research on RO for perchlorate removal has used water from systems in California.

4.3.2 Is it known that regional water quality variations will limit treatment effectiveness or reliability in some areas?

No. Although most of the existing research is for a limited region, there are no data indicating that regional water quality variations will limit effectiveness or reliability. As discussed under Question [REF _Ref525296057 \r \h], water quality affects the design (e.g., concentrate volume, cleaning frequency, antiscalant selection, temperature) of an RO system, but not its effectiveness or reliability.

4.3.3 Are there any regional issues with respect to residuals handling or water resource use?

The large volume of water "lost" as RO residuals can be an issue in regions where water scarcity is a concern. The Small Business Advocacy Review Panel [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"gdtGpwWB","properties":{"formattedCitation":"(1999)","plainCitation":"(1999)","noteIndex":0},"citationItems":[{"id":1032,"uris":["http://zotero.org/groups/945096/items/UPXK6DUI"],"uri":["http://zotero.org/groups/945096/items/UPXK6DUI"],"itemData":{"id":1032,"type":"report","title":"Report of the Small Business Advocacy Review Panel on EPA's Planned Proposal of the National Primary Drinking Water Regulation for Arsenic","author":[{"literal":"Small Business Advocacy Review Panel"}],"issued":{"date-parts":[["1999"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] pointed out that a water rejection rate of 20 to 25 percent can present a problem where water is scarce, such as in the western states. The availability of discharge options for residuals is also a region- and system-specific issue, depending on location, climate, and state and local regulations. The technology is more likely to be feasible when ocean discharge or evaporation ponds are an option.

4.3.4 Is additional research needed?

No. Additional research is not required.

4.4 Compatibility of Reverse Osmosis with Other Treatment

Processes

4.4.1 Have the effects (adverse or beneficial) of the treatment process on other processes likely to be present at existing plants been evaluated?

Yes. Adverse effects are unlikely. RO might have some effect on treated water chemistry (see Question [REF _Ref297723336 \r \h]), which might alter corrosion control or blending requirements. Generally, however, these effluent chemistry changes should not require significant adjustments to downstream treatment processes. With regard to beneficial effects, RO membranes can remove a wide range of contaminants, including inorganic ions, total dissolved solids, nitrate, radionuclides, total organic carbon, some disinfection byproduct precursors, and synthetic organic chemicals. Since RO permeate has a reduced chlorine demand, its finished water requires a low dose of disinfectant.

4.4.2 Will additional pre- or post-treatment be required for integration into an existing (or planned) treatment train?

Yes. Post-treatment is typically required to control corrosion impacts (see Question [REF _Ref297723336 \r \h]).

4.4.3 Is additional research needed?

No. Additional research is not required.

4.5 Ability of Reverse Osmosis to Bring all of the Water System into Compliance

4.5.1 Will perchlorate treatment affect the distribution system or water resource decisions?

Yes. The permeate from RO filtration is essentially deionized water, and generally requires post treatment for corrosion control before it enters a distribution system [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ESfj3Lck","properties":{"formattedCitation":"(American Water Works Assocation and American Society of Civil Engineers (AWWA/ASCE), 2005)","plainCitation":"(American Water Works Assocation and American Society of Civil Engineers (AWWA/ASCE), 2005)","noteIndex":0},"citationItems":[{"id":998,"uris":["http://zotero.org/groups/945096/items/KMLLX76Z"],"uri":["http://zotero.org/groups/945096/items/KMLLX76Z"],"itemData":{"id":998,"type":"book","title":"Water Treatment Plant Design","publisher":"AWWA","publisher-place":"Denver, CO","edition":"4th","event-place":"Denver, CO","author":[{"literal":"American Water Works Assocation and American Society of Civil Engineers (AWWA/ASCE)"}],"issued":{"date-parts":[["2005"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}]. In other drinking water treatment applications, the permeate is often blended with untreated water to produce a less corrosive finished water. If the source water has a sufficiently low concentration of perchlorate and other contaminants, blending may reduce post-treatment requirements. Thus, distribution system effects can be managed by adjusting corrosion control programs or blending practices.

As discussed under Question [REF _Ref297720638 \r \h], the large volume of RO residuals might have an impact on water resource decisions in regions where water scarcity is a concern.

4.5.2 Might the treatment process, residuals handling, or pre- or post-treatment requirements raise new environmental quality concerns?

Yes. The disposal of large volumes of RO residuals could create an environmental quality concern. As discussed under Question [REF _Ref297720638 \r \h], discharge concerns are region- and system-specific.

4.5.3 Is additional research needed?

No. Additional research is not required.

4.6 Reasonable Cost Basis for Reverse Osmosis for Large and Medium Systems

4.6.1 Is the technology currently used by medium and large systems (including uses for other treatment purposes)?

Yes. Although there are no known full-scale RO facilities specifically for the removal of perchlorate, there are a large number of medium and large systems that use RO for other contaminants.

4.6.2 Do the treatment studies provide sufficient information for design assumptions?

Relevant design parameters for RO include:

- Flux rate
- Membrane type
- Membrane array configuration
- Recovery rate
- Pretreatment requirements
- Cleaning procedures.

Assumptions about these parameters for RO, in general, are determined based on major water quality parameters, such as hardness parameters, chloride, sulfate, silica, pH, silt density index, and total dissolved solids. They typically are not affected by trace contaminant influent concentrations or removal requirements. There is nothing unique about perchlorate removal by RO that suggests a different relationship between the major water quality parameters and typical design requirements.

4.6.3 Is additional research needed?

No. Additional research is not required.

5 Summary of Best Available Technology Evaluation

[REF _Ref330451823 * MERGEFORMAT] provides a summary of the evaluation results for the three technologies against each of the criteria. Based on this evaluation, the overall conclusions are:

- Ion exchange is a potential BAT. It has been show to achieve high removal efficiency for perchlorate, particularly with the use of perchlorate-selective resin. It is a mature and established technology in general and has been used for full-scale treatment of perchlorate at a large number of facilities. The use of disposable perchlorate-selective resins eliminates concerns about large volumes of liquid residuals in the form of spent regenerant.

- Biological treatment is a potential BAT. It has been shown to achieve high removal efficiency for perchlorate, including at a full-scale fluidized bed drinking water treatment facility. The technology may, however, need to be used in conjunction with post-treatment processes to ensure finished water quality and mitigate distribution system impacts. Water temperatures also may restrict the technology's applicability on a regional or system-specific basis.

- RO is a potential BAT. It has been shown to achieve high removal efficiency for perchlorate at bench- and pilot-scale. Although no full-scale results are available specifically for perchlorate, RO is a mature and established technology in general. Scale-up of RO systems depends primarily on major water quality parameters and is not dependent on the characteristics of trace contaminants like perchlorate. Large volumes of residual concentrate, however, will likely restrict the technology's applicability on a system-specific basis. Additional research on treatment of perchlorate-bearing RO residuals could help mitigate this issue in some cases.

Exhibit [SEQ Exhibit * ARABIC]. Perchlorate Technologies Evaluated Against BAT Criteria

Criterion	Ion Exchange	Biological Treatment	Reverse Osmosis
1. High Removal Efficiency			
1.1. Have high removal efficiencies that achieve potential MCLs been documented?	Yes	Yes	Yes
1.2. Are the effects of water quality parameters on treatment effectiveness and reliability well-known?	Yes	Yes	Yes
1.3. Is the technology reliable enough to continuously meet a drinking water MCL?	Yes	Depends on temperature	Yes
1.4. Is additional research needed?	No	No	No
2. History of Full-Scale Operation			
2.1. Do existing studies include full-scale operations at drinking water treatment facilities?	Yes	Yes (using fluidized bed reactors)	Yes (for other treatment purposes)
2.2. Are there studies of full-scale treatment of residuals that fully characterize residual waste streams and disposal options?	Yes	Yes	Yes (for other treatment purposes)
2.3. Can the bench or pilot studies be scaled up to represent full-scale treatment, including residuals generation and handling?	Yes	Yes	Yes
2.4. Is additional research needed?	No	No	Maybe
3. General Geographic Applicability			
3.1. What regions do the existing research studies represent?	Primarily California	Primarily California	Primarily California
3.2. Is it known that regional water quality variations will limit treatment effectiveness or reliability in some areas?	No	Yes	No
3.3. Are there any regional issues with respect to residuals handling or water resource use?	Not likely	No	Yes
3.4. Is additional research needed?	No	No	No
4. Compatibility with Other Treatment Processes			
4.1. Have the effects (adverse or beneficial) of the treatment process on other processes likely to be present at existing plants been evaluated?	Yes	Yes	Yes
4.2. Will additional pre- or post-treatment be required for integration into an existing (or planned) treatment train?	Possibly	Yes	Yes
4.3. Is additional research needed?	No	No	No
5. Ability to Bring All of the Water System into Compliance			
5.1. Will the treatment process adversely affect the distribution system or water resource decisions?	Possibly	Yes	Yes
5.2. Might the treatment process, residuals handling, or pre- or post-treatment requirements raise new environmental quality concerns?	Not likely	Yes	Yes
5.3. Is additional research needed?	No	Maybe	No
6. Reasonable Cost Basis for Large and Medium Systems			
6.1. Is the technology currently used by medium and large systems (including uses for other treatment purposes)?	Yes	Yes	Yes (for other treatment purposes)
6.2. Do the treatment studies provide sufficient information on design assumptions to allow cost modeling?	Yes	Yes	Yes
6.3. Is additional research needed?	No	No	No

6 Small System Compliance Technology Evaluation

6.1 SSCT Analysis Method

A technology must be both effective and affordable to be designated an SSCT. Technologies that meet the effectiveness criterion include those designated as BATs for the proposed rule: anion exchange, biological treatment, and centralized RO. For an MCL greater than or equal to 4 micrograms per liter (µg/L), certified POU RO devices also meet the effectiveness criterion.[3]

To evaluate affordability, EPA compared incremental costs per household for each perchlorate-removal technology against an *expenditure margin*. [REF _Ref326056084 \h * MERGEFORMAT] shows the expenditure margins for each system size category. It also shows how EPA derived the expenditure margins, beginning with estimates of MHI, which vary by system size category. The annual affordability threshold for household expenditures on drinking water is 2.5 percent of MHI. EPA deducted estimates of baseline or current water bills from the affordability threshold to obtain the expenditure margin estimates.

Exhibit [SEQ Exhibit * ARABIC]. Expenditure Margins for SSCT Affordability Analysis

System Size (Population Served)	Median Household Income[1] (a)	Affordability Threshold[2] (b) = 2.5% x a	Baseline Water Cost[3] (c)	Expenditure Margin (d) = b - c
25-500	$52,791	$1,320	$341	$979
501-3,300	$51,093	$1,277	$395	$883
3,301-10,000	$55,975	$1,399	$412	$987

Notes:
1. MHI based on U.S. Census 2010 American Community Survey (ACS) 5-year estimates [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"fjCG5GoK","properties":{"formattedCitation":"(U.S. Census Bureau, 2010)","plainCitation":"(U.S. Census Bureau, 2010)","noteIndex":0},"citationItems":[{"id":1017,"uris":["http://zotero.org/groups/945096/items/WJ35QNBT"],"uri":["http://zotero.org/groups/945096/items/WJ35QNBT"],"itemData":{"id":1017,"type":"article","title":"American Community Survey, 5-year Estimates (2006-2010)","author":[{"family":"U.S. Census Bureau","given":""}],"issued":{"date-parts":[["2010"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] stated in 2010 dollars, adjusted to 2017 dollars using the CPI (for all items) for areas under 50,000 persons.
2. Affordability threshold equals 2.5 percent of MHI.
3. Household water costs derived from 2006 Community Water System Survey [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"X3nlQwhM","properties":{"formattedCitation":"(USEPA, 2009)","plainCitation":"(USEPA, 2009)","noteIndex":0},"citationItems":[{"id":262,"uris":["http://zotero.org/groups/945096/items/DZNAAV6M"],"uri":["http://zotero.org/groups/945096/items/DZNAAV6M"],"itemData":{"id":262,"type":"article","title":"2006 Community Water System Survey - Volume II: Detailed Tables and Survey Methodology","URL":"https://www.epa.gov/dwstandardsregulations/community-water-system-survey","author":[{"literal":"USEPA"}],"issued":{"date-parts":[["2009",5]]},"accessed":{"date-parts":[["2018",8,17]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], based on residential revenue per connection within each size category, adjusted to 2017 dollars based on the CPI (for all items) for areas under 50,000 persons.

[3] POU RO devices that are certified as meeting NSF/ANSI Standard 58 have demonstrated an ability to reduce perchlorate concentrations from 130 µg/L to 4 µg/L or less ([HYPERLINK "http://www.nsf.org/consumer/drinking_water/perchlorate_reduction.asp"]). As of August 2018, there is no standard for POU anion exchange devices.

The cost per household varies by technology and by system size category. EPA used the following method to estimate per-household costs using EPA's work breakdown structure (WBS) technology cost models:

- Estimate system-level costs for capital expenditures and annual operating and maintenance (O&M) costs
- Estimate daily design flow and average flow based on median population
  - Estimate capital cost using a technology-specific WBS cost curve and design flow
  - Estimate O&M costs using a WBS cost curve and average flow
- Calculate annual total costs (annualized capital expenditures plus O&M costs)
- Divide total annual costs by the median number of households served.

The WBS models generate capital costs based on equipment that can handle peak production levels or design flows. Annual costs are based on average daily flows. [REF _Ref326097745 \h * MERGEFORMAT] shows the design and average flow estimates for the median system in each system size category. It also shows the population served by the median system and the number of households served.

Exhibit [SEQ Exhibit * ARABIC]. Design and Average Flow Estimates and Service Estimates for the 50th Percentile or Median System

System Size (Population Served)	System Population[1] (a)	System Households[2] (b) = a/2.65	Groundwater System Design Flow[3] (MGD)	Groundwater System Average Flow[3] (MGD)	Surface Water System Design Flow[3] (MGD)	Surface Water System Average Flow[3] (MGD)
25-500	110	42	0.049	0.012	0.050	0.015
501-3,300	1,143	431	0.46	0.15	0.46	0.16
3,301-10,000	5,422	2,046	2.0	0.77	2.0	0.74

Notes:
1. Median system populations are from SDWISFED, January 2004.
2. Median system household estimates equal median populations divided by 2.57 persons per household (based on the 2004 U.S. Census mean).
3. Flow estimates are based on regression equations that relate population and design or average flows.

EPA generated costs for each system size category for 38 treatment technology scenarios. There are 12 scenarios for anion exchange comprising all combinations of two source waters (ground and surface), two resin lives (250,000 and 170,000 bed volumes), and three cost levels (low, mid, and high). There are 18 scenarios for biological treatment that are combinations of two source waters, three reactor types (fixed bed pressure vessel, fixed bed gravity basin, and fluidized bed), and three cost levels. There are 6 scenarios for RO utilized as centralized treatment to account for two source waters, and three cost levels, and two design flow ranges. Finally, there are two scenarios for POU RO to account for two source waters. Costs for POU RO do not vary by cost level input (high, mid, low). USEPA [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"2Q4yNirn","properties":{"formattedCitation":"(2018)","plainCitation":"(2018)","noteIndex":0},"citationItems":[{"id":246,"uris":["http://zotero.org/groups/945096/items/VUJUPN7L"],"uri":["http://zotero.org/groups/945096/items/VUJUPN7L"],"itemData":{"id":246,"type":"article","title":"Technologies and Costs for Treating Perchlorate-Contaminated Waters","publisher":"EPA ***-*-*-

****","author":[{"family":"USEPA","given":""}],"issued":{"date-parts":[["2018"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] contains the cost curve parameters for all of the treatment technology scenarios. There are separate parameter sets for capital costs and O&M costs and for small, medium, and large system sizes (corresponding to design flows ranges of < 1.0 MGD, ≥ 1.0 MGD to < 10 MGD, and ≥ 10 MGD).

For each scenario, EPA estimated capital and O&M costs for the three system size categories and then calculated total annual costs. For anion exchange, biological, and central RO treatment technologies, EPA annualized capital costs at 7 percent over the expected useful life of centralized treatment equipment and added the result to O&M costs. For POU RO devices, EPA annualized capital costs (i.e., for the devices and installation) over the estimated 10-year life of the POU device. Finally, EPA divided total annual costs by the number of households served to derive per-household incremental costs for perchlorate treatment. EPA assessed affordability by comparing these values with the expenditure margins.

6.2 Results

[REF _Ref326111577 \h * MERGEFORMAT] provides ranges of per-household costs for each technology and system size category. The ranges indicate minimum and maximum costs across the scenarios noted in the previous section. For each system size category, the per-household cost range for anion exchange is lower than the corresponding expenditure margin in [REF _Ref326056084 \h]. POU RO devices meet the affordability criteria for the two smaller size categories. EPA's WBS model for POU treatment does not cover systems larger than 3,300 people (greater than 1 MGD design flow).

Exhibit [SEQ Exhibit * ARABIC]. Expenditure Margins for SSCT Affordability Analysis

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis
25-500	$378 to $610	$2,146 to $3,709	$2,272 to $2,671	$265 to $271
501-3,300	$98 to $148	$324 to $566	$561 to $688	$250 to $251
3,301-10,000	$104 to $153	$211 to $315	$431 to $493	Not applicable[1]

Note:
1. EPA's WBS model for POU treatment does not cover systems larger than 3,300 people (greater than 1 MGD design flow), because implementing and maintaining a large-scale POU program is likely to be impractical.

The results are mixed for biological treatment and RO. For both technologies, the cost range exceeds the expenditure margin for the smallest system size category. The cost range falls below the expenditure margin for the two larger system size categories. Therefore, biological treatment and centralized RO meet the SSCT criteria for the two larger systems size categories, but not the smallest one. [REF _Ref326100138 \h * MERGEFORMAT] provides a summary of which technologies meet SSCT criteria for the three system size categories.

Exhibit [SEQ Exhibit * ARABIC]. SSCT Affordability Analysis Results – Technologies that Meet Effectiveness and Affordability Criteria

System Size (Population Served)	Ion Exchange	Biological Treatment	Reverse Osmosis	Point-of-Use Reverse Osmosis

25-500	Yes	No	No	Yes
501-3,300	Yes	Yes	Yes	Yes
3,301-10,000	Yes	Yes	Yes	Not applicable[1]

Note:
1. EPA's WBS model for POU treatment does not cover systems larger than 3,300 people (greater than 1 MGD design flow), because implementing and maintaining a large-scale POU program is likely to be impractical.

7 References

[ADDIN ZOTERO_BIBL {"uncited":[],"omitted":[],"custom":[]} CSL_BIBLIOGRAPHY]

United States
Environmental Protection
Agency

Technologies and Costs for Treating Perchlorate-Contaminated Waters

Office of Water (4607M)
EPA ***-*-**-***
November 2018
www.epa.gov/safewater

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[TOC \O "1-2" \H \Z \T "HEADING 3,3"]

List of Exhibits

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List of Abbreviations and Symbols

ANSI	American National Standards Institute
ARA	Applied Research Associates
BAT	best available technology
BPOU	Baldwin Park Operable Unit
BV	bed volumes
CDPH	California Department of Public Health[1]
ClO_4^-	perchlorate anion
DO	dissolved oxygen
EBCT	empty bed contact time
EPA	U.S. Environmental Protection Agency
GAC	granular activated carbon
gfd or gpd/ft^2	gallons per day per square foot
gfd/psi	gallons per day per square foot per pound per square inch
gpm	gallons per minute
gpm/ft^2	gallons per minute per square foot
gpm/ft^3	gallons per minute per cubic foot
HRT	hydraulic residence time
LSI	Langelier saturation index
MCL	maximum contaminant level
µg/L	micrograms per liter
mg/L	milligrams per liter
MGD	million gallons per day
MWH	Montgomery Watson Harza
NDMA	N-nitrosodimethylamine
NF	nanofiltration
NSF	NSF International, The Public Health and Safety Company
O&M	operation and maintenance
ORNL	Oak Ridge National Laboratory
PNDM	Perchlorate and Nitrate Destruction Module
POTW	publicly-owned treatment works
POU	point-of-use
PRB	perchlorate-reducing bacteria
RO	reverse osmosis
SDI	silt density index
SSCT	small system compliance technology
T&C	technology and costs
TDP	Technology Design Panel
TOC	total organic carbon
UF	ultrafiltration
VOC	volatile organic compound
WBS	work breakdown structure

[1] Formerly, the California Department of Health Services

1 Introduction

1.1 Background

The perchlorate anion (ClO_4^-) is an inorganic ion that consists of a tetrahedral array of oxygen atoms around a central chlorine atom. Perchlorate is primarily an anthropogenic contaminant that generally occurs as a perchlorate salt. These salts are used in a wide range of applications, including pyrotechnics and fireworks, blasting agents, matches, lubricating oils, textile dye fixing and so on. Common salts of perchlorate ion are ammonium, potassium, and sodium perchlorate. Ammonium perchlorate, used in rocket and missile propellant, accounts for approximately 90 percent of perchlorate salts production (Xu et al., 2003). These salts are highly soluble in water, and dissociate completely to their cations and anions (perchlorate).

Perchlorate can persist in the environment for many decades under typical groundwater and surface water conditions because of its resistance to reaction with other mutually occurring compounds or elements. The physiochemical properties of perchlorate limit its treatment alternatives. For example, conventional treatment (coagulation and filtration) does not remove perchlorate because it is a poor complexing anion and does not form any complexes easily with other chelating ligands or cations, making it harder to remove perchlorate by chemical precipitation or complexation process.

The U.S. Environmental Protection Agency (EPA) is proposing to regulate perchlorate in drinking water distributed by certain public water systems. In 2011, EPA determined that a national primary drinking water regulation for perchlorate would result in a meaningful opportunity to reduce health risks (USEPA, 2011). Based on the best available scientific information on the health effects of perchlorate, EPA is proposing a maximum contaminant level goal of 56 µg/L and an enforceable MCL of 56 µg/L. EPA is also requesting comment on 18 µg/L for the MCL.

To assist in this evaluating the national costs associated with removing perchlorate, this document describes treatment technologies that have the potential to remove or destroy perchlorate in drinking water. It also presents estimated costs associated with the installation and operation of these technologies. The technologies evaluated here can achieve very high perchlorate removal efficiencies (e.g., 95 percent or greater). Given the high efficiencies, EPA assumes systems will blend treated water and untreated water to meet the MCL. Accordingly, the costs presented here reflect systems designed and operated to take advantage of the technologies' high removal effectiveness and the cost curves should be applied to design and average flows adjusted for blending, as discussed in Chapter [REF _Ref326047741 \r \h].

1.2 Organization and Overview

This report is organized as follows:

- Evaluation of technologies (or other options) for complying with potential perchlorate standards (Chapters [REF _Ref529892564 \r \h] through [REF _Ref529892577 \r \h])
- Costs for treatment technologies (Chapter [REF _Ref326047741 \r \h]).

The technology evaluations in Chapter [REF _Ref529892618 \r \h] through [REF _Ref529892638 \r \h] describe treatment technologies with the potential to remove or destroy perchlorate in drinking water. Specifically, they address treatment effectiveness for the following:

- ion exchange (Chapter [REF _Ref529892648 \r \h])
- biological treatment (Chapter [REF _Ref529892663 \r \h])
- membrane technologies (Chapter [REF _Ref529892673 \r \h])
- point-of-use (POU) treatment (Chapter [REF _Ref529892683 \r \h]).

For each technology, the corresponding chapter provides an overview of how the technology operates and summarizes its effectiveness for removal or destruction of perchlorate. Each technology summary also incorporates available findings with respect to variability under different source water conditions. Information on process waste characterization and management is also provided. Each summary concludes with a compilation of the engineering design specifications available from the documents reviewed.

Chapter [REF _Ref529892703 \r \h] discusses alternative, nontreatment options that might be used in lieu of treatment to comply with potential perchlorate standards. Chapter [REF _Ref326047741 \r \h] (in combination with Appendices B and C) presents estimated costs for installing and operating each of the technologies or options discussed in Chapters [REF _Ref529892737 \r \h] through [REF _Ref529892767 \r \h]. Appendix A presents available information on the potential treatment of residuals from perchlorate removal, a topic that is relevant to several of the technologies. Appendix B provides complete cost equations for the technologies and nontreatment options evaluation. Appendix C presents example cost model outputs for selected flow rates, allowing review of individual cost line items.

1.3 Information Sources

The information presented in this document is a summary of EPA's literature search to evaluate the state of science with respect to treatment alternatives for perchlorate-contaminated drinking source water. The objectives of the literature review were to:

- identify what technologies are being studied and tested
- summarize the evidence regarding effectiveness
- characterize other factors relevant for drinking water treatment (e.g., pre- and post-treatment requirements and waste characterization and management options)
- identify key research gaps.

2 Ion Exchange

2.1 Operating Principle

Ion exchange is a physical/chemical separation process in which an ion such as perchlorate in the feed water is exchanged for an ion (typically chloride) on a resin generally made of synthetic beads or gel. Feed water passes through a bed of resin in a vessel or column. The operation typically continues until the resin does not have sufficient exchange sites available for perchlorate. At this point, the resin may be disposed and replaced or regenerated. Regeneration occurs when the exhausted resin is rinsed with a concentrated chloride solution. Because of the overwhelming concentration, the chloride in the regenerant replaces the adsorbed ions on the resin, returning the resin to its original state.

The fate of perchlorate treated through ion exchange depends on how the spent resin is managed. If the resin is disposed after exhaustion, the perchlorate remains bound to the spent resin. If the resin is regenerated, the perchlorate becomes concentrated in the spent regenerant solution. Perchlorate will be destroyed only if the spent regenerant is further treated (e.g., through physical, chemical, or biological reduction).

Because it is a large, poorly hydrated, hydrophobic anion (see, for example, Gu et al., 2001 and Batista et al., 2002), perchlorate interacts readily with certain types of anion exchange resins, particularly those described as strong-base resins. Several types of resins have the potential to remove perchlorate effectively, at least initially. The key differences among the resins are in their long-term capacity, particularly in the presence of competing anions, and their ease of regeneration. These differences can be significant in terms of the type and quantity of waste generated from the treatment process.

The resin types studied for perchlorate removal include strong-base and weak-base anion resins with polystyrenic, polyacrylic, and polyvinylpyridine matrices, with the most extensive study of strong-base polystyrenic and polyacrylic resins (see, for example, Tripp et al., 2003 and Batista et al., 2000). The category of strong-base polystyrenic resins includes those typically used for removal of nitrate (i.e., "nitrate-selective" resins). In addition, in the early 2000s, researchers at the Department of Energy's Oak Ridge National Laboratory (ORNL) developed a specialized perchlorate-selective resin. Investigators describe this resin as "bifunctional," because it contains two functional groups, one to enhance selectivity and the other to aid kinetics (Batista et al., 2002; Gu et al., 2003). More recently, a number of new, competing perchlorate-selective resins have become available. These include an updated version of the original bifunctional resin, along with other single functional group (often tributylamine) resin formulations (Blute et al., 2006; Russell et al., 2008; Wu and Blute, 2010).

There are significant differences among the strong-base polyacrylic, strong-base polystyrenic, nitrate-selective, and perchlorate-selective resins in terms of their relative affinity for perchlorate (Tripp et al., 2003; Boodoo, 2003; Batista et al., 2002; Darracq et al., 2014). **[REF _Ref286409769 \h * MERGEFORMAT]** categorizes these resins in order of their perchlorate affinity. Although certain resin types have higher relative affinity than others, all of the types shown in **[REF _Ref286409769 \h * MERGEFORMAT]**, along with weak-base resins, are able to remove perchlorate. The key differences among the resins are in their long-term capacity,

particularly in the presence of competing anions, and their ease of regeneration. Because of these differences, the recent literature indicates a trend toward the increased use of perchlorate-selective resins, which are generally disposed of, rather than regenerated. Section [REF _Ref286409819 \r \h] discusses the removal rates achieved by different resin types in more detail. Section [REF _Ref286409855 \r \h] discusses resin capacity in light of raw water quality and Section [REF _Ref286409883 \r \h] covers regeneration needs.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Perchlorate Affinity by Resin Type

Perchlorate Affinity	Resin Type
Lowest affinity	Strong-base polyacrylic
Lower affinity	Strong-base polystyrenic
Higher affinity	Nitrate-selective
Highest affinity	Perchlorate-selective

Conventional ion exchange systems use a fixed resin bed where, after exhaustion of the resin, operators will take a vessel out of service temporarily to either remove and dispose of the spent resin or regenerate the resin.

[REF _Ref286408337 \h * MERGEFORMAT] provides a schematic drawing for a conventional ion exchange system with brine regeneration. With resin disposal, instead of regeneration, as is common for perchlorate-selective resin, the schematic layout becomes simpler. Designs with disposable resin do not require brine storage, eductors, or brine piping. As discussed in Section [REF _Ref286408573 \r \h], another possible option (instead of disposal) for selective resins is to use a novel procedure involving a tetrachloroferrate solution for regeneration. **[REF _Ref286408793 \h * MERGEFORMAT]** provides a schematic drawing for an ion exchange system using disposable resin (i.e., without regeneration).

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Typical Schematic Layout for Perchlorate Removal by Ion Exchange with Brine Regeneration

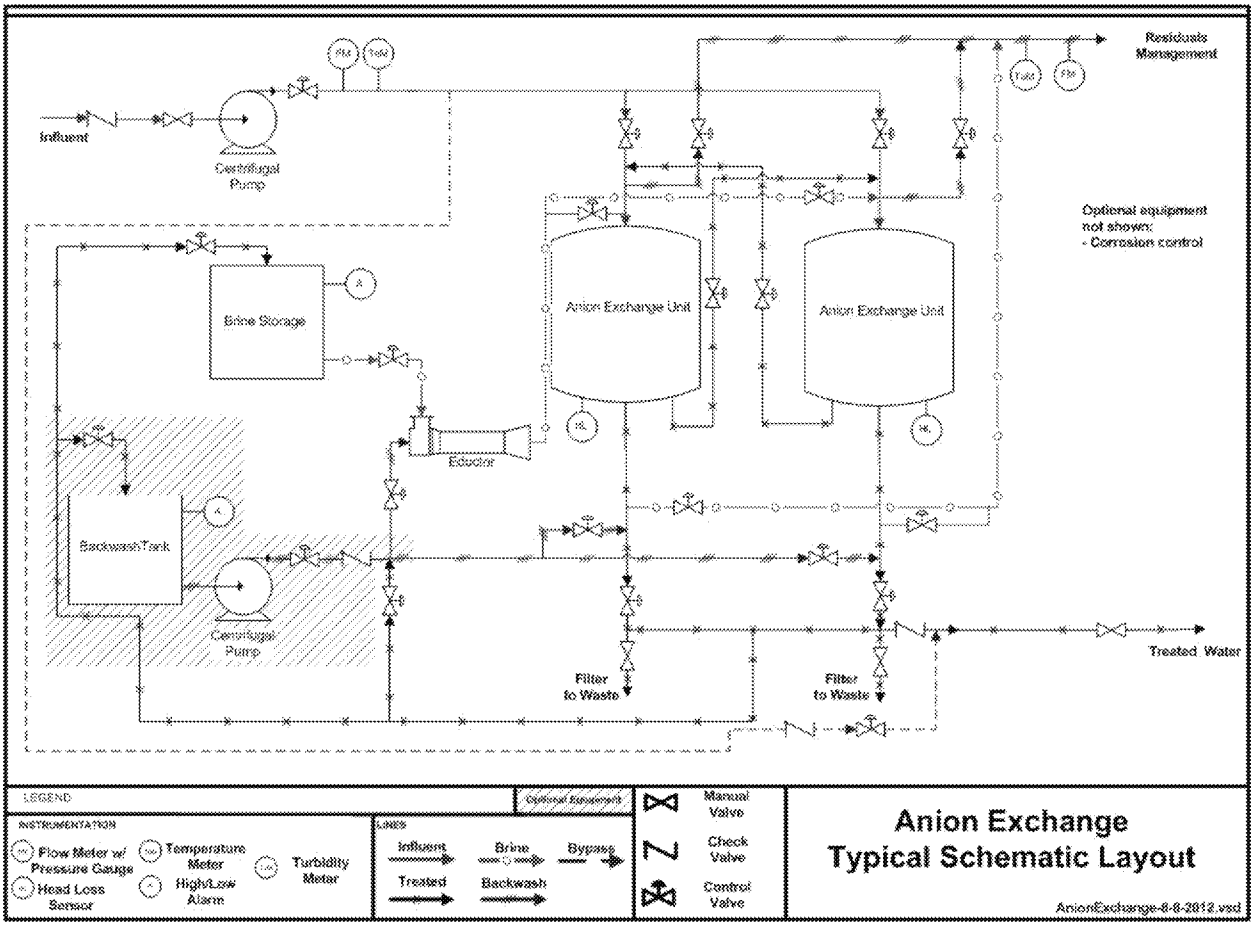
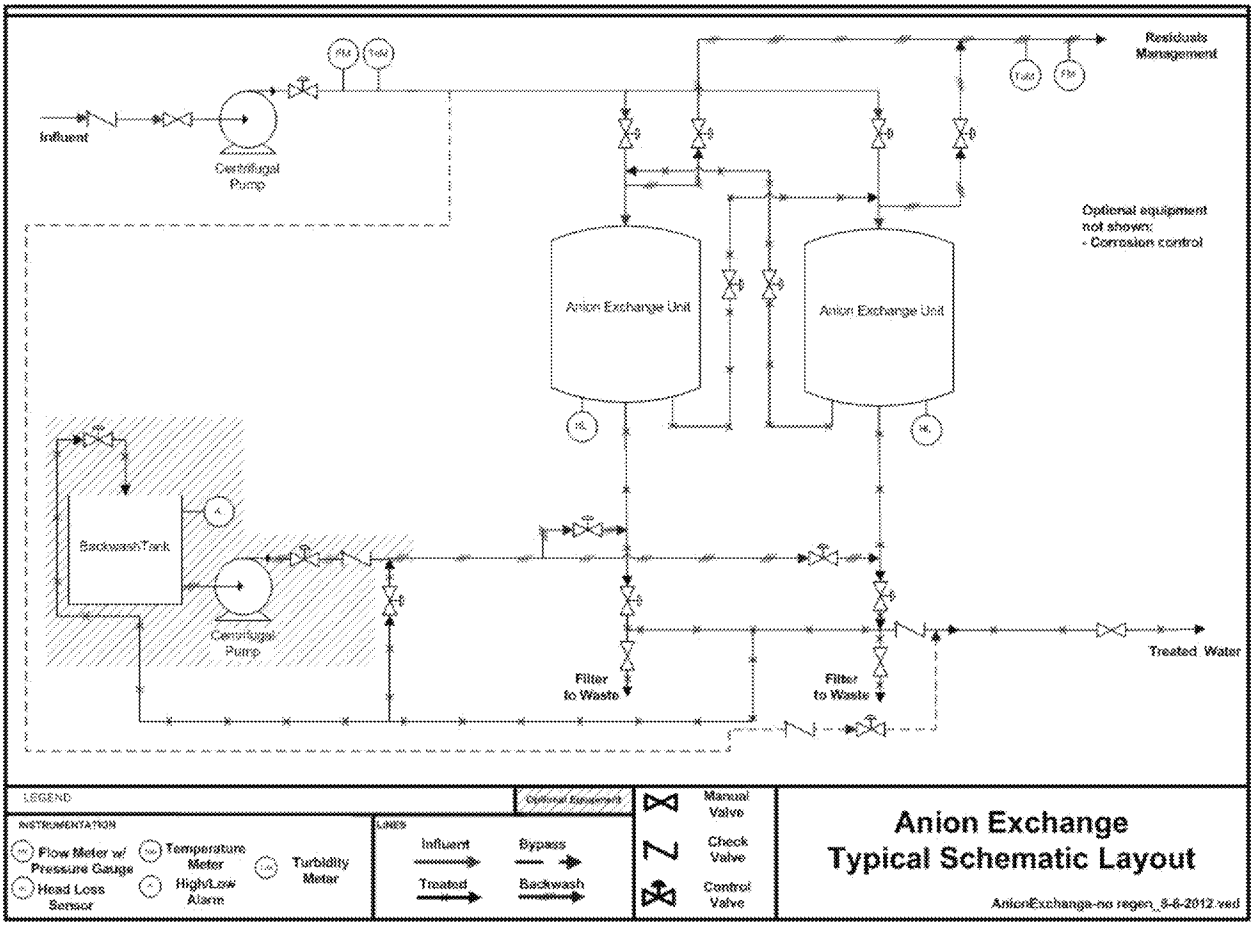


Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Typical Schematic Layout for Perchlorate Removal by Ion Exchange with Resin Disposal



2.2 Effectiveness for Perchlorate Removal

The State of California has identified ion exchange (along with fluidized bed biological treatment) as one of two BATs for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). Researchers have demonstrated that ion exchange is capable of removing perchlorate to levels below 2 to 4 µg/L, even given very high influent perchlorate concentrations. This result corresponds, generally, to a removal efficiency in the 90 percent range, depending on the influent concentration. **[REF _Ref286411328 \h * MERGEFORMAT]** summarizes the removal efficiencies reported in the literature. It includes results from studies conducted in the laboratory, in the field at pilot scale, and in full-scale application.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Perchlorate Effectiveness Results for Ion Exchange

Resin Type[1]	Removal Efficiency	Resulting Concentration (µg/L)	Study Scale[2]	Data Source(s)
SB	>77% to >94%	<4	P	Venkatesh et al., 2000; GWRTAC, 2001
	>95.7% to >97%	<4	F	Praskins, 2003; Berlien, 2003; GWRTAC, 2001
	>97.5% to >98.1%	<2,000	F	Praskins, 2003; GWRTAC, 2001; Wagner and Drewry, 2000
	>98%	<4	P	ITRC, 2008
	>98% and >99.6%	<4	P	Venkatesh et al., 2000; GWRTAC, 2001
SB-S, SB-A, WB-S, WB-A	>99.9%	<20	L	Batista et al., 2000; Batista et al., 2002
NS	>44%	<4	F	CA EPA, 2004
	>60%	<4	F	CA EPA, 2004
	>60%	<4	F	CA EPA, 2004
	>76%	<4	F	ITRC, 2008
	>85% and >96%	<4	P	Burge and Halden, 1999
	>99.3%	<3	P	Gu et al., 1999; Gu et al., 2003
PS	Not specified	<4	F	ITRC, 2008
	>60%	<4	F	ITRC, 2008
	>60% to >73%	<4	F	Hayward and Gillen, 2005; Siemens, 2009b
	>75% to >80%	<2	L, P	Blute et al., 2006
	>82%	<2	P	Lutes et al., 2010
	>83% to >95%	<2	P	Russell et al., 2008
	>84%	<4	P	ITRC, 2008
	>92%	<4	F	ITRC, 2008
	>93.3% to >97.8%	<1	F	Siemens, 2009c; Membrane Technology, 2006
	>94%	<2	P	Wu and Blute, 2010
	>97.5%	<0.35	F	ITRC, 2008
	>98%	<1	P	ITRC, 2008
	>98.6%	<4	F	ITRC, 2008
	>97.6% to >99.2%	<0.5	F	Drago and Leserman, 2011
	>99.3%	<3	P	Gu et al., 1999; Gu et al., 2003
	>99.7%	<3	L	Gu et al., 1999
WB-S	>98.5%	<0.1	P	U.S. DoD, 2008a
	>99.7%	<4	P	U.S. DoD, 2007
Not specified	>60%	<4	F	CA EPA, 2004
	>60% to >98%	<4	F	ITRC, 2008
	>71%	<4	F	ITRC, 2008
	>73%	<4	F	Fontana Water Company, 2010; ITRC, 2008
	>75%	<5	F	Santschi, 2010
	>90%	<2	F	ITRC, 2008
	>96% to >99.7%	<4	L	GWRTAC, 2001
	>99%	<4	F	Siemens, 2009a

Notes:

1. SB = strong-base; SB-S = strong-base polystyrenic; SB-A = strong-base polyacrylic; WB-S = weak-base polystyrenic; WB-A = weak-base polyacrylic; NS = nitrate-selective strong-base polystyrenic; PS = perchlorate selective
2. L = laboratory study; P = field pilot study; F = full-scale

[REF _Ref286411328 \h * MERGEFORMAT] also shows the variety of resin types that have been tested for perchlorate removal. These resin types include strong-base polyacrylic, strong-base polystyrenic (including nitrate-selective), weak-base polyacrylic, weak-base polystyrenic, and perchlorate-selective.[2] All of these resin types can attain very high perchlorate removals, at least initially. While Batista et al. (2000 and 2002) have suggested that weak-base resins may have certain advantages in terms of regenerant treatment (see Section [REF _Ref292709289 \r \h] and Appendix A), tests of these resins have been limited, with only a few studies documented in the reviewed literature (Batista et al., 2000 and 2002; Boodoo, 2006; U.S. DoD, 2007 and 2008a). Furthermore, the use of weak-base resins could require pH adjustment.

Additional support for the effectiveness of ion exchange for perchlorate removal is evident from the number of full-scale facilities that are currently using the technology. As shown in **[REF _Ref286411968 \h * MERGEFORMAT]**, the literature identifies 44 full-scale facilities applying ion exchange for perchlorate removal. **[REF _Ref286411968 \h * MERGEFORMAT]** also demonstrates the increasing use of perchlorate-selective resins. These installations include both remediation sites and facilities producing drinking water.

Currently, the majority of the identified full-scale facilities (18 of 23 facilities where information on resin type is available) currently use perchlorate-selective resins. An additional two facilities are reportedly planning to switch to perchlorate-selective resin (Wu and Blute, 2010; Blute, 2012). Thus, perchlorate-selective resin appears to have become the technology of choice for perchlorate ion exchange facilities.

[2] While Tripp et al. (2003) also examined strong base polyvinylpyridine resins, comparable quantitative data on their removal efficiency are not available.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Full-scale Ion Exchange Installations for Perchlorate

Location	Flow rate (gallons per minute [gpm])	Resin Type[1]	Resin Fate[2]	Start Date	Data Source(s)
Kerr-McGee, Henderson, Nevada	300 to 600	--	D	November 1999 [3]	Min et al., 2003; Praskins, 2003; GWRTAC, 2001; CA EPA, 2003; CA EPA, 2004; Croft, 2004; ITRC, 2008; Roefer, 2013
LaPuente Valley County Water District, California	2,500	PS [9]	D [9]	February 2000	Wagner and Drewry, 2000; GWRTAC, 2001; Min et al., 2003; Berlien, 2003; Praskins, 2003; CA EPA, 2003; Coppola, 2003; CA EPA, 2004; Bull et al., 2004; Pollack, 2004; ITRC, 2008; Russell et al., 2009; Faccini et al., 2016
Lawrence Livermore National Laboratory, Livermore, California	0.7 to 3.5	NS	R	November 2000	CA EPA, 2004; USEPA, 2005; ITRC, 2008
Kerr-McGee, Henderson, Nevada	200 to 560	--	R	March 2002 [4]	Min et al., 2003; Wagner and Drewry, 2000; CA EPA, 2003; CA EPA, 2004; Croft, 2004; USEPA, 2005; ITRC, 2008; Roefer, 2013; Faccini et al., 2016
California Domestic Water Company, Whittier, California	5,000	PS [8]	D	July 2002	Coppola, 2003; Min et al., 2003; Bull et al., 2004; CA EPA, 2004; Pollack, 2004; Blute et al., 2006; ITRC, 2008; Purolite, 2011; Russell et al., 2009
Gage 51-1, City of Riverside, California	2,000	SB-S	D	October 2002	Lu, 2003; CA EPA, 2004; Bull et al., 2004; Pollack, 2004
Tippecanoe, City of Riverside, California	5,000	SB-S	D	December 2002	Min et al., 2003: Lu, 2003; CA EPA, 2004; Bull et al., 2004; Pollack, 2004; USEPA, 2005; ITRC, 2008
R&H System, La Verne, California	--	--	R	2003 or earlier	Min et al., 2003
City of Pomona, California	10,000	NS [10]	R [10]	2003 or earlier	Coppola, 2003; Min et al., 2003; Bull et al., 2004; CA EPA, 2004; USEPA, 2005
Baldwin Park, California	7,000 and 7,500	--	R	2003 or earlier	Min et al., 2003

Location	Flow rate (gallons per minute [gpm])	Resin Type[1]	Resin Fate[2]	Start Date	Data Source(s)
Edwards Air Force Base, Site 285, California	30	PS	R	2003	ITRC, 2008
West San Bernadino Water District, Rialto, California	2,000	PS	D	May 2003	Coppola, 2003; CA EPA, 2003; CA EPA, 2004; Bull et al., 2004; Pollack, 2004; ITRC, 2008
West Valley Water District, San Bernadino, California	2,000	--	D	June 2003	Coppola, 2003; CA EPA, 2004; USEPA, 2005; Siemens, 2009d;
Aerospace Manufacturer, Maryland	20	--	D [7]	October 2003	Siemens, 2009a
Wells 15, 17, and 24, City of Colton, California	3,600	PS	D	August 2003	Bull et al., 2004; CA EPA, 2004; Xiong and Zhao, 2004; ITRC, 2008
Airport Treatment Plant, City of Rialto, California	2,000	PS	D	August 2003	Coppola, 2003; CA EPA, 2004; Bull et al., 2004; Purolite, 2011
Delta Treatment Plant, City of Monterey Park, California	4,050	--	D	July 2003	Coppola, 2003; CA EPA, 2003; CA EPA, 2004; Pollack, 2004
Santa Clara Valley Water District	--	--	D	Prior to December 2003	Coppola, 2003
Colony and County Wells, West San Martin Water Works, West San Martin, California	800	NS	D	2004 or earlier	CA EPA, 2004; Bull et al., 2004; USEPA, 2005; ITRC, 2008
Texas Street, City of Redlands, California	1,100	PS	D	2004	City of Redlands, 2004; Bull et al., 2004; ITRC, 2008
Fontana Union Water Co., Fontana, California	6,000	PS	D	January 2004	CA EPA, 2004; USEPA, 2005; ITRC, 2008; Fontana Water Company, 2010
Castaic Lake Water Agency, Whittaker, California	300	PS [11]	D [11]	Prior to March 2004	Bull et al., 2004; USEPA, 2005; Blute, 2012
City of Morgan Hill, California	400 to 1,000	--	D	Prior to March 2004 [5]	Bull et al., 2004; CA EPA, 2004; USEPA, 2005; Russell et al., 2009
Big Dalton Well, San Gabriel Water Quality Association, Baldwin Park, California	3,000	--	--	Prior to March 2004	Bull et al., 2004
Camping World, San Martin County Water District, California	2,000	--	--	Prior to March 2004	Bull et al., 2004

Location	Flow rate (gallons per minute [gpm])	Resin Type[1]	Resin Fate[2]	Start Date	Data Source(s)
Southern California Water Co., South San Gabriel, California	750	--	--	Prior to March 2004	Bull et al., 2004
Fontana (F17 site), San Gabriel Valley Water Company, El Monte, California	5,000	PS	D	Prior to March 2004	Bull et al., 2004; Lutes et al., 2010 ; Purolite, 2011
B6 Well Site, San Gabriel Valley Water Company, El Monte, California	7,800	-- [6]	R [6]	May 2004	CA EPA, 2003; CA EPA, 2004; Pollack, 2004; Russell et al., 2009
Valley County Water District, Baldwin Park, California	7,800	-- [6]	R [6]	June 2004	Coppola, 2003; CA EPA, 2003; CA EPA, 2004; Pollack 2004; Russel et al., 2009
Jet Propulsion Laboratory, Pasadena, California	1,400	--	D	July 2004	USEPA, 2005
Aerojet, Sacramento, California	400 to 2,000	PS	D [7]	August 2004	CA EPA, 2004; USEPA, 2005; ITRC, 2008; Purolite, 2011
Lincoln Avenue Water Co., Altadena, California	2,000	PS	D [7]	August 2004	Hayward and Gillen, 2005; Siemens, 2009b; ITRC, 2008
Frank Perkins Road Treatment System, Massachusetts Military Reservation, Cape Cod, Massachusetts	300	--	--	September 2004	USEPA, 2005
B5 Well Site, San Gabriel Valley Water Company, El Monte, California	7,800	PS	D	December 2004	CA EPA, 2004; Pollack, 2004; Purolite, 2011
Phoenix Goodyear Airport North, City of Goodyear, Arizona	440	--	D	2005	ITRC, 2008
Aquarion Water Co., Millbury, Massachusetts	1,500	PS	D [7]	June 2005	Siemens, 2009c; Membrane Technology, 2006
California Water Services Company, Porterville, California	--	--	D	April 2006	Siemens, 2006
Camp Edwards portion of the Massachusetts Military Reservation, Cape Cod, Massachusetts	1,000	PS	D	2007	ITRC, 2008
Naval Weapons Industrial Reserve Plant, McGregor, Texas	--	--	D	2008 or earlier [3]	ITRC, 2008

Location	Flow rate (gallons per minute [gpm])	Resin Type[1]	Resin Fate[2]	Start Date	Data Source(s)
Arrowhead Regional Medical Center, Colton, California	600	--	--	January 2010	Water & Wastes Digest, 2010
Saugus Perchlorate Treatment Facility, Castaic Lake Water Agency, Santa Clarita, California	2,200	PS	D	May 2010	Drago and Leserman, 2011
Richardson Treatment Plant, Loma Linda, California	1,200	--	--	October 2010	Santschi, 2010
Monk Hill Water Treatment Plant, Pasadena Water and Power, Pasadena, California	7,000	PS	D	July 2011	Erdman, 2011; Blute, 2012
Golden State Water Service	2,000	PS	D	2011 or earlier	Purolite, 2011

Notes:
-- = Not reported
1. SB-S = strong-base polystyrenic; SB-A = strong-base polyacrylic; NS = nitrate-selective strong-base polystyrenic; PS = perchlorate-selective
2. D = Disposed; R = Regenerated
3. No longer in operation (replaced with biological reactor).
4. Discontinued after 6 months due to operational issues.
5. Inactive as of March 2004.
6. Reportedly planning to switch to use of perchlorate-selective resin with disposal instead of regeneration (Wu and Blute, 2010).
7. Specifically, spent resin at this facility is incinerated.
8. Switched from strong-base polystyrenic resin to perchlorate-selective resin as of 2011 (Purolite, 2011; Wu and Blute, 2010).
9. Switched from strong-base polyacrylic resin to perchlorate-selective resin with disposal instead of regeneration in July 2010 (Blute, 2012).
10. Currently installing perchlorate-selective resin in addition for part of the treatment train (Blute, 2012).
11. Installed perchlorate-selective resin beginning in 2011 (Blute, 2012).

2.3 Raw Water Quality Considerations

The most significant raw water quality consideration in ion exchange perchlorate treatment is the concentration of competing anions (particularly sulfate, nitrate, bicarbonate, and chloride). The effect of these anions is to decrease a resin's longer-term capacity to adsorb perchlorate, as they compete with perchlorate for exchange sites. Resin capacity (also termed resin life or run length) typically is measured by the number of bed volumes (BV) of water that can be treated before breakthrough of perchlorate. Competing anions take up available exchange sites, reducing perchlorate capacity. In addition, these anions may break through or peak[3] before perchlorate, affecting finished water quality and limiting the practical life of the resin more than perchlorate capacity alone. For example, Case et al. (2004) reported that a strong-base polyacrylic resin could treat 750 BV before perchlorate breakthrough. Nitrate peaking, however, would limit the use of the resin to 425 BV. In practice, however, systems can limit the impact of peaking by using multiple treatment trains in parallel. Also, the full-scale facility studied in Drago and Leserman (2011) eliminated chloride peaking by converting the resin from a chloride to a bicarbonate form prior to installation.

There are significant differences among resin types in terms of the relative impact of competing anions. This impact is related to the relative affinity of the resin for each anion present. **[REF _Ref286412546 \h * MERGEFORMAT]** shows quantitative data from the literature on BV to perchlorate breakthrough for different resin types in the presence of differing concentrations of the major competing anions. The data shown in **[REF _Ref286412546 \h * MERGEFORMAT]** are for initial detection of perchlorate (at detection limits between 1 and 4 µg/L, depending on the specific study) using a single resin column. After perchlorate breakthrough, most resins still have the capacity to continue adsorbing perchlorate before the resin is completely saturated. In practice, using two columns in series (a "lead-lag" configuration) can capture this extra capacity (Boodoo, 2003). For example, Gu et al. (1999) found breakthrough in a lead column after 8,500 BV for a nitrate-selective resin and 40,000 BV for a perchlorate-selective resin. Using a second (lag or polishing) column increased the resins' capacities to approximately 22,000 BV and 104,000 BV, respectively.

Precise, quantitative comparisons of the data in **[REF _Ref286412546 \h * MERGEFORMAT]** are difficult because of variations among studies (e.g., influent concentrations of perchlorate and other constituents, definition of breakthrough, and specific resin manufacturer). The data, however, when combined with general conclusions in the literature, do allow for some general observations about differences among resin types.

[3] Peaking occurs when competing anions adsorbed early in a resins life are displaced by perchlorate, resulting in an effluent concentration of the competing anions greater than the influent concentration. See Boodoo (2003) for an example of peaking behavior.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Perchlorate Capacity by Resin Type and Competing Anions

Resin Type[1]	Data Source(s)	Perchlorate Capacity (BV to breakthrough)	Competing Anions (mg/L)			
			Sulfate	Nitrate[2]	Bicarbonate	Chloride
SB-A	Batista et al., 2000 and 2002	1,800 to 2,100	None	None	None	None
	Case et al., 2004	750	Present	Present	Present	No data
	Tripp et al., 2003	700	50	6	122	30
	Min et al., 2003	700	55	27	155	15
	Boodoo, 2003	500	44	40	170	13
	Lehman et al., 2008	650	56	63	300	25
	Batista et al., 2000 and 2002	0[3]	>2,000	>40	No data	No data
SB-S	Batista et al., 2000 and 2002	3,750	None	None	None	None
	Tripp et al., 2003	6,000	50	6	122	30
	Boodoo, 2003	5,000	44	40	170	13
	Batista et al., 2000 and 2002	600[3]	>2,000	>40	No data	No data
NS	Batista et al., 2000	1,300	None	None	None	None
	Gu et al., 2003	14,000	173	3.2	226	356
	Tripp et al., 2003	25,000[4]	50	6	122	30
	Gu et al., 1999	8,500	14.9	61.2	No data	7.0
PS-Old	Gu et al., 2003	40,000	173	3.2	226	356
	Tripp et al., 2003	35,000[3]	50	6	122	30
	Min et al., 2003	20,700	266	14	229	40
	Gu et al., 1999	40,000	14.9	61.2	No data	7.0
	Gu et al., 2007	37,000	16	10	No data	10
	Lutes et al., 2010	97,000	14.8	32.8	192	10.7
	Blute et al., 2006	~75,000	46.4	1.6	No data	No data
PS-New	Blute et al., 2006	~160,000	46.4	1.6	No data	No data
	Russell et al., 2008	~130,000 to 170,000	37	25	No data	23
	Russell et al., 2008	~125,000 to 140,000	44	33	No data	27
	Russell et al., 2008	~105,000 to 130,000	53	61	No data	47
	Wu and Blute, 2010	~130,000	45	33	No data	No data
	Drago and Leserman, 2011	~30,000 to 60,000	130 to 220	18	No data	17 to 29
WB-S	Batista et al., 2000	500	None	None	None	None
	U.S. DoD, 2007	3,000 to 4,000	3	4	No data	4
	U.S. DoD, 2008a	9,700	14	31	150	11
	Boodoo, 2006	15,000	No data	No data	No data	No data
WB-A	Batista et al., 2000 and 2002	2,700 to 2,800	None	None	None	None
	Batista et al., 2000 and 2002	800 to 1,000	100	100	None	100

Notes:

1. SB-S = strong-base polystyrenic; SB-A = strong-base polyacrylic; WB-S = weak-base polystyrenic; WB-A = weak-base polyacrylic; WB = weak-base (type not specified); NS = nitrate-selective strong-base polystyrenic; PS-Old = original perchlorate-selective resin developed by ORNL; PS-New = more recently developed perchlorate-selective resins.
2. as NO3.
3. The presence of humic substances caused reduced resin capacity.
4. Column fouling (due to experimental design) may have caused reduced resin capacity.

2.3.1 Strong-base Polyacrylic Resins

The order of affinity of strong-base polyacrylic resins is as follows (Boodoo, 2003; Gu et al., 2001):

sulfate > perchlorate > nitrate > chloride > bicarbonate

Accordingly, Tripp et al. (2003) and Boodoo (2003) conclude that the capacity of strong-base polyacrylic resins is most significantly affected by sulfate concentration. Using computer modeling, Tripp et al. (2003) predicted an 88 percent decrease in strong-base polyacrylic capacity as influent sulfate increased from 1 to 250 milligrams per liter (mg/L). The decrease in capacity was rapid as sulfate increased (see Tripp et al., 2003, Figure 4.61). The cross-study data in **[REF _Ref286412546 \h * MERGEFORMAT]** are consistent with this prediction. For this resin type, Batista et al. (2000 and 2002) found a perchlorate capacity of 1,800 to 2,100 BV for a laboratory solution with no sulfate. In comparison, sulfate concentrations in the range of 40 to 60 mg/L reduced capacity to 500 to 700 BV in other studies (Case et al., 2004; Tripp et al., 2003; Min et al., 2003; Boodoo, 2003; Lehman et al., 2008). Batista et al. (2000 and 2002) found that very high sulfate concentrations (greater than 2,000 mg/L) prevented a polyacrylic resin from removing any perchlorate (i.e., a capacity of 0 BV), although the investigators suggest fouling of the resin as a contributing factor to the decreased capacity.

Tripp et al. (2003) predicted that strong-base polyacrylic resins are not as sensitive to increasing nitrate concentrations (see Tripp et al., 2003, Figure 4.62). Capacity decreased linearly by 36 percent as influent nitrate increased from 0.1 to 20 mg/L as N (Tripp et al., 2003). Again, the cross-study data support this conclusion, finding similar capacities (500 to 700 BV) for nitrate concentrations from 6 to 63 mg/L as NO_3 (Case et al., 2004; Tripp et al., 2003; Min et al., 2003; Boodoo, 2003; Lehman et al., 2008).

2.3.2 Strong-base Polystyrenic Resins

The order of affinity of strong-base polystyrenic resins is as follows (Boodoo, 2003; Gu et al., 2001):

perchlorate > sulfate > nitrate > chloride > bicarbonate

Therefore, the capacity of strong-base polystyrenic resins should be affected by sulfate concentration, but to a lesser degree than that of polyacrylic resins. Using computer modeling, Tripp et al. (2003) predicted a 94 percent decrease in strong-base polystyrenic capacity as influent sulfate increased from 1 to 250 mg/L. The decrease in capacity, however, was not as rapid as for the polyacrylic resin. Interpolation of Figure 4.61 in Tripp et al. (2003) shows a capacity decrease of approximately 60 percent for the polystyrenic resin at 50 mg/L sulfate, compared to a decrease of nearly 80 percent for the polyacrylic resin. Similarly, the cross-study data in **[REF _Ref286412546 \h * MERGEFORMAT]** show a relatively high perchlorate capacity (5,000 to 6,000 BV) for strong-base polystyrenic resins at moderate sulfate concentrations (40 to 50 mg/L) (Tripp et al., 2003; Boodoo, 2003).

Tripp et al. (2003) predicted that strong-base polystyrenic resins, like polyacrylic resins, are not as sensitive to increasing nitrate concentrations (see Tripp et al., 2003, Figure 4.62). Capacity decreased linearly by 26 percent as influent nitrate increased from 0.1 to 20 mg/L (Tripp et al.,

2003). The cross-study data are consistent with this observation, finding similar capacities (5,000 to 6,000 BV) for nitrate concentrations from 6 to 40 mg/L (Tripp et al., 2003; Boodoo, 2003).

2.3.3 Nitrate-Selective Resins

The order of affinity of nitrate-selective resins is as follows (Boodoo, 2003; Burge and Halden, 1999):

perchlorate > nitrate > sulfate > chloride > bicarbonate

Accordingly, computer modeling performed by Tripp et al. (2003) found these resins affected by both sulfate and nitrate, with the greater effect caused by nitrate. Nitrate-selective capacity for perchlorate decreased by 76 percent as nitrate increased from 0.1 to 20 mg/L, compared to 64 percent for a sulfate increase from 1 to 250 mg/L (Tripp et al., 2003). The cross-study data in **[REF _Ref286412546 \h * MERGEFORMAT]** appear consistent, if one ignores an anomalous data point from Batista et al. (2000). Capacities shown are 25,000 BV for moderate sulfate and moderate nitrate (Tripp et al., 2003), 14,000 BV for high sulfate and low nitrate (Gu et al. 2003), and 8,500 BV for low sulfate and high nitrate (Gu et al. 1999).

2.3.4 Perchlorate-Selective Resins

As discussed in Section [REF _Ref529882092 \r \h], researchers at ORNL developed the first perchlorate-selective resin in the early 2000s. This original, bifunctional resin was known as "BiQuat" and licensed to Purolite for sale under the name Purolite A530E (Boodoo, 2003). More recently, a number of new, competing perchlorate-selective resins have become commercially available. These include (U.S. Filter, 2004; Russell et al., 2008; Blute et al., 2006; Wu and Blute, 2010; Drago and Leserman, 2011; Darracq et al., 2014):

- Purolite A532E (an updated version of the old A530E resin)
- Purolite MCG-P2
- Resin Tech SIR-110-HP
- Rohm & Haas PWA2
- Dow PSR2
- Calgon CalRes 2109.

The order of affinity of the original perchlorate-selective resin was the same as that for nitrate-selective resins (i.e., perchlorate > nitrate > sulfate > chloride), but the perchlorate affinity relative to nitrate affinity was nearly an order of magnitude greater (Boodoo, 2003). Boodoo (2003) suggested that this original resin would be negatively affected by high nitrate concentrations. The cross-study data in **[REF _Ref286412546 \h * MERGEFORMAT]**, however, suggest that the resin was not, in fact, very sensitive to competing anions. Capacity remained high (20,700 to 97,000 BV) for a wide range of nitrate and sulfate concentrations (1.6 to 61.2 mg/L and 14.8 to 266 mg/L, respectively) (Gu et al., 2003; Tripp et al., 2003; Min et al., 2003; Gu et al., 1999; Gu et al., 2007; Lutes et al., 2010; Blute et al., 2006).

For the more recently developed perchlorate-selective resins, the data in **[REF _Ref286412546 \h * MERGEFORMAT]** generally show significantly greater perchlorate capacity than the original resin. In the presence of moderate levels of both sulfate and nitrate, the new resins showed capacities of approximately 105,000 to 170,000 BV (Blute et al., 2006; Russell et al.,

2008; Wu and Blute, 2010). Even at higher sulfate levels, at least one of the new resins showed equal or greater capacity than the older resin (Drago and Leserman, 2011). The differences in capacity among the individual new resins appear to be less significant than the difference between the new resins as a group and the old resin. In the studies shown in **[REF _Ref286412546 \h * MERGEFORMAT]** (Blute et al., 2006; Russell et al., 2008; Wu and Blute, 2010; Drago and Leserman, 2011), different resins performed better depending on variations in specific competing anions and other site-specific conditions (i.e., no one of the new resins was consistently superior to the others in all of the studies).

2.3.5 Weak-base Resins

As shown in **[REF _Ref286412546 \h * MERGEFORMAT]**, researchers have conducted only limited study on the effect of competing anions on the perchlorate capacity of weak-base resins. Sulfate and nitrate reduce the capacity of weak-base polyacrylic resins when they are present at relatively high levels (100 mg/L each) (Batista et al., 2000; Batista et al., 2002). Data are not available, however, on the effect of more moderate levels of competing anions. Batista el al. (2000) reported that weak-base polystyrenic resins have a relatively low capacity (500 BV) even absent competing anions. Pilot tests at Redstone Arsenal in Alabama used a weak-base polystyrenic resin produced by Purolite. This resin achieved 15,000 BV (Boodoo, 2006), 3,000 to 4,000 BV (U.S. DoD, 2007), or 9,700 BV (U.S. DoD, 2008a) capacity, depending on the test conditions. U.S. DoD (2008a) suggested that competing ions such as nitrate would reduce the capacity of this resin, but data are not available on the magnitude of such competitive effects.

2.3.6 Raw Water Quality Considerations other than Sulfate and Nitrate Competition

Although most investigators identify bicarbonate and chloride as other major competing anions, the affinity of ion exchange resins for these anions is less than that for perchlorate, sulfate, and nitrate. Therefore, their impact on resin perchlorate capacity would be expected to be less than that of sulfate and nitrate. There are, however, no quantitative data in the literature on the effects of these major anions. Similarly, U.S. DoD (2002) indicates that raw water pH can strongly influence treatment effectiveness, but no quantitative data are available.

Other co-contaminants that may affect perchlorate capacity include arsenic (Tripp et al., 2003; Berlien, 2003), uranium (Tripp et al., 2003; Min et al., 2003), and chromium (Min et al., 2003). Based on the high affinity of most resins for perchlorate, direct competition from these co-contaminants would be expected to be low. Accumulation of these contaminants in high concentrations on the resin or in regenerant solution may affect disposal (see Section [REF _Ref286414613 \r \h]), limiting the practical life of a resin. For example, Tripp et al. (2003) suggests that a perchlorate-selective resin would require regeneration every 10,000 BV to prevent arsenic and uranium build-up. Recent studies of various perchlorate-selective resins, however, have shown that build-up of metals results in concentrations that are below regulatory limits that would require disposal as a hazardous waste, both under federal requirements and California's more stringent limits (Russell et al., 2008; Blute et al., 2006; Wu and Blute, 2010). The same studies found that uranium build-up might require special handling as a radioactive waste in only one of the 12 samples tested (total across all three studies). In some cases, however, incineration facilities have facility-specific restrictions on uranium concentrations that are more stringent that the regulatory thresholds for radioactive waste.

2.4 Pre- and Post-Treatment Needs

Suspended solids and organic substances in source water can cause clogging or fouling of ion exchange resins (U.S. DoD, 2002; Batista et al., 2002; Gu et al., 2003). For example, Batista et al. (2002) found that high concentrations of humic substances (as measured by total organic carbon [TOC]) caused fouling of both strong-base polyacrylic and polystyrenic resins, interfering with perchlorate removal. In spite of earlier conclusions that the perchlorate-selective bifunctional resin would require no pre-treatment (Gu et al., 1999; ORNL, 2002), in pilot testing of the resin, Gu et al. (2003) found that precipitation and/or deposition of iron oxyhydroxides and microbial biomass caused significant clogging and fouling of the resin columns. The addition of a fine in-line filter resolved the problem. Similarly, the full-scale system studied in Drago and Leserman (2011) included pre-treatment bag filters and sulfuric acid addition to minimize scaling. Therefore, the presence of suspended solids and organic matter may require the use of filtration and/or chemical addition as pretreatment. Although the literature reviewed for this report does not identify the specific conditions under which filtration is needed (e.g., concentration of total suspended solids), these conditions are expected to be similar to those documented in application of ion exchange treatment for other contaminants. For perchlorate-selective resins, pre-filtration (bag or cartridge filters) may be required regardless of water quality because the long run lengths (see Section [REF _Ref350336683 \r \h]) can result in greater solids accumulation.

Batista et al. (2000) indicates that weak-base resins require carbonation to treat perchlorate. Carbonation can be accomplished by adding carbon dioxide or bicarbonate (generated by feeding sodium bicarbonate through a strong-acid cationic resin) to the feed. Thus, carbonation may constitute a pre-treatment step required for the use of weak-base resins. More information is required on the need for and practicality of this step to evaluate the use of weak-base resins. The weak-base resin piloted in Alabama requires pH reduction with carbon dioxide or acid as a pre-treatment step, carbon dioxide removal as a post-treatment step, and pH adjustment, if needed, as a post-treatment step (Boodoo, 2006; U.S. DoD, 2007 and 2008a). An operational pH between 3 and 5, with a target of 4, is required for this resin to operate effectively (U.S. DoD, 2007 and 2008a).

Ion exchange treatment can increase the corrosivity of treated water (Betts, 1998; Berlien, 2003; U.S EPA, 2005) because of the addition of chloride ions and/or removal of carbonates and bicarbonates. Berlien (2003) reports this problem with a full-scale application of ion exchange for perchlorate treatment. Treated water had a pH of approximately 7 and created red water problems in older homes with galvanized steel pipe. The operators corrected this problem by adding sodium hydroxide to raise the pH to approximately 8.2 and adding polyphosphates as an additional protection measure. For applications of weak-base resins where pre-treatment pH adjustment would be required, increasing the pH after treatment would also be necessary for corrosion control.

Tripp et al. (2003) and Min et al. (2003) indicate that N-nitrosodimethylamine (NDMA) may form within certain polystyrenic resins and leach into the treated water. Recent studies of perchlorate-selective resins (Russell et al., 2008; Blute et al., 2006; Wu and Blute, 2010; Drago and Leserman, 2011) have shown leaching of various nitrosamines at first flush or soon after startup, with levels that decline to below detection over time (four hours to one week, depending

on the specific resin and nitrosamine). Thus, nitrosamine leaching appears to occur periodically and temporarily (e.g., after installation of new resin). Issues with nitrosamine leaching might be avoided if resins are sufficiently flushed prior to use. For example, the full-scale system studied in Drago and Leserman (2011) minimized nitrosamine leaching with changes to the manufacturer's pre-delivery rinsing and preparation procedures. For one resin, however, Wu and Blute (2010) suggest that rinsing longer than manufacturer recommendations may be required to eliminate leaching concerns. Blute et al. (2006) also hypothesize that nitrosamines could be eliminated by downstream processes such as ultraviolet light treatment, if present.

2.5 Waste Generation and Residuals Management Needs

After a resin reaches its perchlorate capacity (see Section [REF _Ref286414835 \r \h]), the operator must either dispose and replace the resin or regenerate the resin using a chemical solution to remove the adsorbed anions. The former option, commonly termed "throwaway" operation, generates solid waste in the form of spent resin loaded with perchlorate and other anions. The latter option generates a liquid waste in the form of spent regenerant with concentrated perchlorate and other anions. Both options can also generate liquid waste in the form of spent wash water when initial flushing is required upon installation of new resin (e.g., to prevent nitrosamine leaching, see Section [REF _Ref350937116 \r \h]). As shown in **[REF _Ref286411968 \h * MERGEFORMAT]**, almost 79 percent (30 of 38) of full-scale facilities for which waste management data are available dispose of spent resin. This statistic includes all but one of the full-scale facilities using perchlorate-selective resin. An additional two facilities are reportedly planning to switch away from regeneration to disposal of spent resin (Wu and Blute, 2010; Blute, 2012).

2.5.1 Disposal

In systems using resin disposal without regeneration, calculation of the quantity of solid waste generated would be straightforward, based on the quantity of resin used and the life of the resin. Spent resin characteristics depend on resin type, influent water quality, and the life of the resin. As discussed in Section [REF _Ref286658749 \r \h], studies of metals build-up in perchlorate-selective resins have found that these resins are not likely to meet regulatory definitions of hazardous waste (Russell et al., 2008; Blute et al., 2006; Wu and Blute, 2010). Because of the shorter life of conventional resins, metals accumulation in these resins likely would be even lower and, thus, the same result should hold true. A typical destination for non-hazardous spent resin would be disposal in an off-site landfill. Based on the data in **[REF _Ref286411968 \h * MERGEFORMAT]**, however, at least four of the full-scale facilities appear to be sending their spent resin to incineration facilities.

2.5.2 Regeneration

In systems using regeneration, the characteristics and quantity of spent regenerant depend on the type of regenerant solution used. The type of regenerant solution selected depends, in turn, on the type of resin used. In addition, the quantity of spent regenerant can be reduced if the regenerant is treated and reused. Appendix A discusses regenerant treatment.

In conventional ion exchange processes using strong-base resins (i.e., for removal of arsenic), operators regenerate spent resin using a brine solution of concentrated sodium chloride or potassium chloride. For resins loaded with perchlorate, however, regeneration with brine is more

difficult because of the high relative affinity of most resins for perchlorate. In general, the higher the perchlorate affinity of a resin (see **[REF _Ref286409769 \h * MERGEFORMAT]**), the more difficult it is to regenerate using conventional brine solutions. For example, Tripp et al. (2003) found that regeneration required a significantly greater quantity of brine solution for strong-base polystyrenic resins than for strong-base polyacrylic resins. Similarly, Batista et al. (2000) were able to successfully regenerate a perchlorate-loaded strong-base polyacrylic resin with 12 percent sodium chloride, removing 96 percent of the loaded perchlorate. In comparison, they found regeneration of a nitrate-selective resin using the same solution very ineffective, removing only 17.3 percent of the loaded perchlorate. Investigators, therefore, suggest that highly perchlorate-selective resins cannot be regenerated at all using conventional regenerant solutions (Boodoo, 2003; Gu et al., 2001; Gu et al., 2003; Batista et al., 2000; Darracq et al., 2016).

Regeneration of Non-selective Strong-Base Resins

It appears that, while regeneration of non-selective resins using brine solutions is feasible, large quantities of spent regenerant may result. Although polyacrylic resins regenerate easily, they have relatively short run lengths (see Section [REF _Ref286415007 \r \h]) and, therefore, more frequent regeneration. On the other hand, while polystyrenic resins have longer run lengths, they require more regenerant. Based on computer modeling, Tripp et al. (2003) conclude that the polyacrylic resins are more efficient in terms of quantity of spent regenerant as a percentage of water treated. In practice, regeneration may be accomplished using partial exhaustion-partial regeneration. In this scenario, operators regenerate the resin well before perchlorate breakthrough (e.g., at the point of sulfate or nitrate breakthrough) and regenerate using smaller quantities of brine than would be required for complete perchlorate removal. This practice allows operation for a number of cycles until perchlorate builds up on the resin and complete regeneration is required, and may result in lower overall generation of spent regenerant.

Tripp et al. (2003) suggest partial exhaustion-partial regeneration operation for pilot testing of non-selective resins. Results of tests of this approach reported by Case et al. (2004) suggest that partial exhaustion-partial regeneration is effective, at least for the strong-base polyacrylic resin, with no change in performance for over 20 cycles.

Based on the designs reported in Montgomery Watson Harza (MWH) and University of Houston (2003) and Case et al. (2004), spent regenerant generation in the pilot tests would be 1.5 to 1.6 percent of treated water (6.4 BV of regenerant/400 to 425 BV of treated water) for the polyacrylic resin and 1.4 percent of treated water (9 BV of regenerant/625 BV of treated water) for the polystyrenic resin.[4] Data on spent regenerant generation are not available for the full-scale operations using conventional treatment configurations, although Betts (1998) reports that conventional processes (for contaminants other than perchlorate) typically generate 2 to 5 percent brine waste.[5]

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[4] These estimates are for a conventional treatment configuration, as opposed to an ISEP design, and do not account for additional brine waste generated at the time of complete regeneration.

[5] In comparison, a full-scale ISEP design, using its continuous regeneration approach, reportedly generates 1% brine waste in practice (Berlien, 2003).

One option for increasing the efficiency of regenerating strong-base polystyrenic resins may be heating the regenerant brine. Based on laboratory experiments, Tripp et al. (2003) found that perchlorate affinity decreases with increasing temperature for these resins. Based on these results and computer modeling, they concluded that heating the brine to 40 degrees centigrade would make the polystyrenic resins equivalent to the polyacrylic resins in terms of quantity of spent regenerant as a percentage of water treated. Heating to 60 degrees centigrade would make the polystyrenic resins more efficient than the polyacrylic resins.

Spent brine generated from the regeneration of perchlorate-loaded resins contains high concentrations of perchlorate. Spent brine might be expected to contain 1.5 to 3.0 mg/L of perchlorate (Case et al., 2004).[6] The high perchlorate concentrations may mean that the waste must be treated prior to disposal. Regenerant treatment can have an additional advantage in that it may allow for reuse of the regenerant multiple times, reducing the quantity of waste generated. Appendix A discusses regenerant treatment in more detail.

Spent brine also contains high levels of the competing anions present in the influent water (nitrate, sulfate, and bicarbonate) (Batista et al., 2002; Berlien, 2003; MWH and University of Houston, 2003). The presence of bicarbonate, in particular, can have practical implications for waste management. A full-scale system in LaPuente, California, experienced scaling problems in the waste line due to elevated levels of carbonates and bicarbonates. The operator began adding hydrochloric acid to the line to lower pH from approximately 8.5 to approximately 7 and remedy the problem (Berlien, 2003). Case et al. (2004) also reported that regular maintenance to prevent the build-up of scale was needed in pilot tests.

Regeneration of Selective Resins[7]

Selective resins are difficult to regenerate and are generally disposed of, rather than regenerated. As discussed above and shown in **[REF _Ref286411968 \h * MERGEFORMAT]**, the majority of the full-scale ion exchange systems, including all but one of those using perchlorate-selective resin, operate on a throwaway basis. Because of the difficulty regenerating selective resins using conventional brine solutions, researchers at ORNL have developed a regeneration process for these resins. The process uses tetrachloroferrate anions ($FeCl_4^-$), formed in a ferric chloride solution in the presence of an excess amount of hydrochloric acid or chloride. Because it also has a strong relative affinity, the tetrachloroferrate anion readily displaces perchlorate from the resin. The tetrachloroferrate anion, however, also decomposes rapidly as the chloride concentration in solution decreases, converting to positively charged iron species. The positively charged iron species desorb from the resin by charge repulsion, leaving the resin in its original state with chloride as the counter anion. After tetrachloroferrate regeneration, the resin must be rinsed with dilute hydrochloride acid to wash sorbed ferric ions and excess regenerant off the bed (Gu et al., 2003; Gu et al., 2001). This rinse is necessary to ensure complete removal of the ferric

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[6] Data are for a conventional treatment system, Berlien (2003) estimates 2 to 4 mg/L of perchlorate for regenerant from an ISEP system.

[7] Note that, because it is an emerging technology with as yet limited full-scale application, the novel tetrachloroferrate regeneration approach discussed in this section is not among the scenarios modeled for cost estimating purposes in Chapter [REF _Ref326047741 \r \h].

ions to prevent precipitation of iron oxyhydroxides that may clog the bed when the resin is reused for treatment after regeneration (Gu et al., 2001).

Gu et al. (2003 and 2001) conducted laboratory-scale and small-scale field pilot tests of this regeneration technology for two types of resin: a commercial nitrate-selective resin and the perchlorate-selective bifunctional resin. They found that nearly complete regeneration could be achieved with as little as two BV of regenerant solution (Gu et al., 2003). They also found no significant deterioration in resin performance after repeated loading and regeneration cycles (Gu et al., 2001). On the basis that the perchlorate-selective bifunctional resin could treat 40,000 BV before breakthrough, they calculated spent regenerant generation at less than 0.005 percent of water treated (Gu et al., 2003). For the nitrate-selective resin, the comparable generation rate would be 0.014 percent (based on the 14,000 BV to breakthrough they reported for this resin). Note that these generation rates do not include the dilute acid rinse required following regeneration, which the investigators report requires 20 to 30 BV of less than 0.01 percent hydrochloric acid (Gu et al., 2001; Gu et al., 2003).

Like conventional brine solutions, spent tetrachloroferrate regenerant is expected to contain high concentrations of perchlorate. Gu et al. (2003) found that perchlorate concentration peaked at 6,000 mg/L in the regenerant from the nitrate-selective resin and 60,000 mg/L in the regenerant from the perchlorate-selective bifunctional resin. As for conventional brine solutions, these high concentrations indicate that treatment of the spent regenerant may be required before disposal or reuse. Batista et al. (2002) expect that the spent tetrachloroferrate regenerant would also contain other competing anions, low pH, and high concentrations of iron in the form of Fe^{+3}, which could have implications for treatment. Appendix A discusses regenerant treatment. Gu et al. (2003) did not detect perchlorate in the dilute hydrochloric acid rinse solution. They suggest that this solution could be neutralized with dilute sodium hydroxide and readily mixed with the treated water or discharged to a publicly owned treatment works.

The ORNL researchers have examined this novel regeneration technology in small-scale field pilot tests (Gu et al., 2003 and 2005). Full-scale application reportedly began at Edwards Air Force Base in January 2003 (U.S. DoD, 2002), but no data are available on results at this installation. More recently, Lutes et al. (2010) reported on a field demonstration of the tetrachloroferrate regeneration approach using full-scale vessel. This study not only involved a larger scale application than the previous work by Gu et al. (2003 and 2005), but also slightly different parameters (e.g., more bed volumes of tetrachloroferrate, fewer bed volumes of dilute acid).

More recently, laboratory studies have examined the use of biological treatment to remove perchlorate from exhausted ion exchange resins. Although these studies suggest that bioregeneration has the potential to be effective for selective resins, the research has not yet progressed beyond batch experiments (Sharbat and Batista, 2013; Faccini et al., 2016).

Regeneration of Weak-base Resins

Batista et al. (2000; 2002) state that the primary advantage of weak-base resins is that they can potentially be regenerated using caustic solutions (sodium hydroxide or ammonium hydroxide), instead of conventional brine solutions. They suggest that this is an advantage because such solutions may be more amenable to biological treatment. In laboratory tests, they demonstrated

that, while a caustic solution was ineffective in regenerating a weak-base polystyrenic resin, weak-base polyacrylic resins could be regenerated easily using 1 percent sodium hydroxide, removing more than 76.5 percent of loaded perchlorate (Batista et al., 2000). Although Batista et al. (2002) suggest that caustic solutions used for regenerating weak-base resins would have high pH (greater than 11) and high ammonium concentration (if ammonium hydroxide is used), they have not published further data on the quantity or characteristics of these spent regenerant solutions.

Boodoo (2006) indicates that the weak-base resin piloted in Alabama could be regenerated using a caustic solution, followed by neutralization/protonation of the resin bed with an acid solution. The quantity of spent caustic solution was estimated to be less than 0.004 percent of water treated. Later tests showed that the weak-base resins were effectively regenerated using volumes of regenerant equal to less than 0.03 percent to less than 0.05 percent of water treated (U.S. DoD, 2007 and 2008a).

2.6 Critical Design Parameters

Critical design parameters that are specific to ion exchange systems removing perchlorate are:

- Resin type
- Vessel configuration (i.e., number of vessels in series)
- Empty bed contact time (EBCT)
- Resin bed life
- Surface loading rate
- Regeneration parameters.

[REF _Ref286650075 \h * MERGEFORMAT] shows values for these parameters used in pilot- and full-scale systems removing perchlorate. Design data are available in the literature for only a few of the many full-scale conventional ion exchange applications. Therefore, much of the data presented in **[REF _Ref286650075 \h * MERGEFORMAT]** are from pilot-scale tests or are for proposed scale-up units.[8]

The paragraphs below discuss each of the parameters listed **[REF _Ref286650075 \h * MERGEFORMAT]** in more detail. Values for other ion exchange design parameters (e.g., resin density, resin expansion during backwash, resin loss during backwash and regeneration), while not specifically addressed in the literature reviewed here, are well documented for ion exchange treatment in general. EPA has no reason to expect a significant difference in these parameters for ion exchange systems treating perchlorate. This section provides a general discussion of the design parameters and the range of values reported in the literature for these parameters. Chapter [REF _Ref326047741 \r \h] identifies the specific values for each parameter used in EPA's cost estimates.

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[8] The data shown are for conventional (rather than ISEP) treatment configurations only. Because of its proprietary nature, available design data for ISEP are limited. Furthermore, facilities developed since 2004 are not using ISEP for perchlorate removal. Finally, data for ISEP systems would not be applicable in models that simulate conventional ion exchange configurations.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Critical Design Parameters for Ion Exchange Systems

Ion Exchange Critical Design Parameter	Value from the References
Resin Type	See text.
Vessels Configuration	Lead-lag configuration in all full-scale applications for which data are available (Lu, 2003; Siemens, 2009a; Siemens, 2009d; Siemens, 2009b; Fontana Water Company, 2010; Drago and Leserman, 2011). Lead-lag configuration in pilot tests and field demonstrations (Boodoo, 2006; Lehman et al., 2008; U.S. DoD, 2008a; U.S. DoD, 2007; ITRC, 2008). Gu et al. (1999) recommend lead-lag configuration in proposed scale-up unit. Tripp et al. (2003) assume parallel operation in model plant designs for cost estimation, but recommend lead-lag design for nitrate-selective or perchlorate-selective resins.
Empty Bed Contact Time	**Conventional Resins**: 6 minutes per vessel in full-scale application at the City of Riverside (Lu, 2003). 2.5 to 4.2 minutes per vessel in model plant designs used for cost estimation (Tripp et al., 2003). 1.5 minutes per column in field pilot tests (MWH and University of Houston, 2003; Lehman et al., 2008). 4 to 6 minutes per column in laboratory column tests (Batista et al., 2000). **Nitrate-selective and Perchlorate-selective Resins:** One resin manufacturer recommends 1.5 minutes per vessel for nitrate-selective resin in full-scale applications (Boodoo, F. Personal communication. March 2, 2006). 1 minute per column in small-scale field pilot tests of perchlorate-selective resins (Gu et al., 2003). 45 seconds per vessel in proposed scale-up unit for perchlorate-selective resins (Gu et al., 1999). 1.5 minutes per column in pilot tests of perchlorate-selective resins (Blute et al., 2006; Russell et al., 2008; Wu and Blute, 2010).
Resin bed life	Dependent on resin type and competing anion concentrations. See text.
Surface loading rate	**Conventional Resins:** Maximum 9 to 15 gpm per square foot (gpm/ft^2) in model plant designs used for cost estimation (Tripp et al., 2003). 19 gpm/ft^2 in field pilot tests (MWH and University of Houston, 2003). 9.7 gpm/ft^2 in pilot tests (U.S. DoD, 2008a). **Perchlorate-selective Resins:** 40 to 50 gpm/ft^2 in proposed scale-up unit (Gu et al., 1999). 12 gpm/ft^2 in pilot tests (Blute et al., 2006; Russell et al., 2008; Wu and Blute, 2010).

Ion Exchange Critical Design Parameter	Value from the References
Regenerant loading rate and application time	**Strong-base Polyacrylic Resins:** 3 to 6% sodium hydroxide at 25 lbs/ft^3 for 45 minutes followed by 3 BV of rinse in field pilot tests (MWH and University of Houston, 2003). 30 lbs/ft^3 in model plant designs used for cost estimation (Tripp et al., 2003). 6% sodium hydroxide at 25 lbs/ft^3 in pilot tests (Lehman et al., 2008). **Strong-base Polystyrenic Resins:** 6% sodium hydroxide at 35 lbs/ft^3 for 63 minutes followed by 3 BV of rinse in field pilot tests (MWH and University of Houston, 2003). 36 lbs/ft^3 for partial regeneration and 400 lbs/ft^3 for full regeneration in model plant designs used for cost estimation (Tripp et al., 2003). **Perchlorate-selective Resins:** 2 to 4 BV of tetrachloroferrate followed by 20 to 30 BV of dilute hydrochloric acid followed by rinse with water or dilute bicarbonate (no data on loading rates) in small-scale field pilot tests (Gu et al., 2003). 6 BV of tetrachloroferrate, 14 BV of dilute hydrochloric acid, 21 BV rinse with water/ dilute bicarbonate in field demonstration (Lutes et al., 2010).

Resin Type

As discussed in Section [REF _Ref286657733 \r \h], a variety of resin types have been tested for perchlorate removal. The selection of resin type will affect most other critical design parameter values. **[REF _Ref286650075 \h * MERGEFORMAT]** and the paragraphs below present data for all major resin categories. As discussed in Section [REF _Ref286657611 \r \h] and shown in **[REF _Ref286411968 \h * MERGEFORMAT]**, however, perchlorate-selective resin appears to have become the technology of choice for modern perchlorate ion exchange facilities when perchlorate is the only contaminant of concern. Thus, where possible, the discussion focuses on parameters specific to perchlorate-selective resins.

Vessel Configuration

Ion exchange vessels can be configured in series or in parallel. In a parallel configuration, one or more vessels are in use, while other vessels are being regenerated or are on standby (Clifford, 1999). Influent water to be treated is divided equally among the operational vessels. Systems set in parallel are generally used to increase throughput. For contaminants that are difficult to remove (such as perchlorate), however, a series configuration can be effective to achieve a greater resin bed life (Boodoo, 2003; Gu et al., 1999). A series configuration allows for operation of the first vessel to a later point on the breakthrough curve because the second vessel can capture the initial breakthrough concentrations from the first vessel, keeping the final treated water from the system below a specified target concentration. As discussed above, series configurations are also known as "lead-lag" designs. As shown in **[REF _Ref286650075 \h * MERGEFORMAT]**, series (lead-lag) operation is generally recommended for perchlorate removal.

Empty Bed Contact Time

EBCT is defined as the volume of resin, including voids, divided by the flow rate. The minimum EBCT required varies depending on the specific contaminant treated, the required contaminant

removal percentage, the type of resin used, and other influent water characteristics (e.g., the presence of competing chemical species). In general, the EBCT for ion exchange removal of conventional anions (e.g., sulfates, nitrates, arsenic) usually ranges between 1.5 and 7 minutes per vessel. As shown in **[REF _Ref286650075 \h * MERGEFORMAT]**, recommended EBCTs for perchlorate removal using conventional resins span this range, mostly falling in the middle to upper end of the range. Selective resins (particularly perchlorate-selective resins), however, remain effective at higher flow rates, which correspond to shorter EBCTs. For example, perchlorate-selective resins can be employed at flow rates of 0.5 to 4 BV per minute (Gu et al., 1999; Gu et al., 2001; Gu et al., 2003). Correspondingly, recommended EBCTs for perchlorate-selective resins shown in **[REF _Ref286650075 \h * MERGEFORMAT]** are 1.5 minutes per vessel and less.

Surface Loading Rate

Loading rate is the velocity of flow through the resin measured in units of flow rate per unit area (e.g., gpm/ft^2). The surface area of the treatment pressure vessels must be selected to maintain loading rates within reasonable bounds. As shown in **[REF _Ref286650075 \h * MERGEFORMAT]**, perchlorate-selective resins may have the potential to remain effective at higher maximum loading rates than conventional resins, although the data remain somewhat uncertain.

Resin Bed Life

Section [REF _Ref286654638 \r \h] provides a detailed discussion of resin capacity (or bed life), which varies depending on resin type and water quality. **[REF _Ref286412546 \h * MERGEFORMAT]** in that section shows detailed data from the literature on resin life. The capacities presented in **[REF _Ref286412546 \h * MERGEFORMAT]** can be extended by series (lead-lag) operation. On the other hand, these capacities can be limited by breakthrough or peaking of co-contaminants.

Regeneration Parameters

Regeneration parameters determine the concentration and quantity of chemicals (i.e., chloride brine or tetrachloroferrate solution) required to restore a resin's capacity to remove perchlorate. They also determine the quantity of waste regenerant generated. As discussed in Section [REF _Ref286653866 \r \h], regeneration requirements depend on the type of resin used. **[REF _Ref286650075 \h * MERGEFORMAT]** shows the available data on regeneration parameters that might be applicable if a system chose to regenerate its resin. As discussed in Section [REF _Ref286658589 \r \h] and shown in **[REF _Ref286411968 \h * MERGEFORMAT]**, however, the majority of full-scale ion exchange systems operate on a throwaway basis.

3 Biological Treatment

3.1 Operating Principle

Biological treatment of perchlorate is the process by which bacteria are used to reduce perchlorate to chlorate, chlorite, chloride, and oxygen. Biological treatment offers complete destruction of the perchlorate ion, eliminating the need for management of perchlorate-bearing waste streams. While there have been a wide variety of laboratory and pilot-scale tests exploring perchlorate treatment using bioreactors, the number of full-scale designs is still very limited.

The fundamental physical and chemical nature of perchlorate complicates the biological treatment process. Common reducing agents do not reduce perchlorate, and common cations do not precipitate it (Urbansky, 1998). Despite its strength as an oxidizing agent, the perchlorate ion is slow to react due to the presence of the highly-oxidized central halogen atom, chlorine (VII). This low reactivity, however, is a matter of kinetics rather that thermodynamics. Urbansky (1998) reports the standard half reactions for reductions to chloride (Eq 1) and chlorate (Eq 2) are favorable processes from a thermodynamic standpoint:

Eq 1 [EMBED Equation.3]

Eq 2 [EMBED Equation.3]

Therefore, the key to reducing perchlorate is finding the right catalyst. Coates et al. (2000) report that the scientific literature has evidence of the microbially-catalyzed reduction of chlorine oxyanions (a group to which perchlorate belongs) dating back over half a century. More recently, Coates et al. (2000), Logan (2001), and others have enumerated perchlorate-reducing bacteria (PRB) in a broad spectrum of environments nationwide, and demonstrated that the microbial reduction of perchlorate is a much more ubiquitous and diverse metabolism than previously considered.

According to Xu et al. (2003), researchers have isolated and characterized many PRB. These microorganisms are all facultative anaerobes and are capable of reducing both perchlorate and chlorate to chloride for energy and growth. Although reduction does not take place (or at least not very quickly) in the presence of a high concentration of dissolved oxygen (DO), most PRB isolates can use oxygen as a terminal electron acceptor. Many PRB partially or completely reduce nitrate. The presence of nitrate usually decreases the rate of perchlorate reduction (until the nitrate is depleted). Most PRB do not reduce sulfate, and none (thus far) use Fe(III), another common component of ground water, as an electron acceptor. Marqusee (2001) presented a summary of electron acceptor use in groundwater samples collected from several locations with varying levels of nitrate (<1.2 to 59 mg/L), perchlorate (9.8 to 666 mg/L), and sulfate (15 to 1,620 mg/L). Generally, the microbial consortia preferred these electron acceptors in the following order:

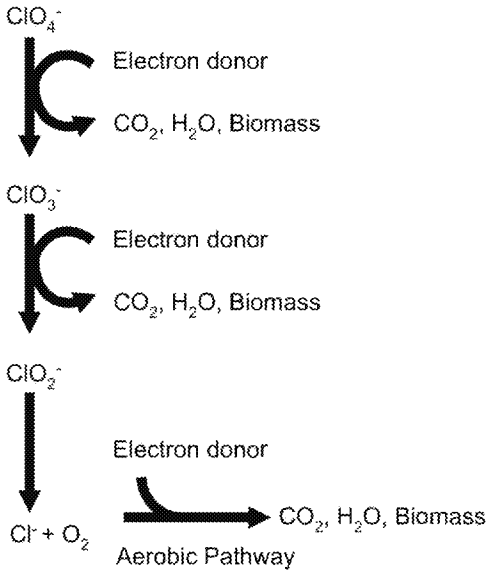
nitrate > perchlorate > sulfate

Researchers have isolated both heterotrophic and autotrophic PRB (Xu et al., 2003). Many studies have used acetate or ethanol as a single substrate (also referred to as the electron donor or "food") for heterotrophic perchlorate reduction; however, optimal substrate use is strain-

dependent. Many studies have also used supplemented nitrogen and phosphorus as necessary nutrients for the growth of PRB. There is no definitive information on what trace nutrients or metals are needed for growth. In one instance reported in Xu et al. (2003), researchers found iron, molybdenum, and selenium in purified perchlorate reductase. Chadhuri et al. (2002) established that the PRB *Dechlorosoma suillum* did not reduce perchlorate without the presence of molybdenum. Several field studies presented later in this chapter achieved perchlorate degradation simply through the addition of an oxidizable substrate (e.g. acetate or ethanol) and nitrogen and phosphorous.

[REF _Ref286664846 \h * MERGEFORMAT] represents the three-step mechanism now widely accepted for bacterial respiration using perchlorate, which sequentially produces chlorate, chlorite, and chloride and oxygen (Xu et al., 2003). While researchers believe *perchlorate reductase* and *chlorite dismutase* are the central enzymes catalyzing the reactions, they are not sure if PRB use these enzymes exclusively or use a broader range of enzymes for perchlorate and chlorate reduction.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Biological Perchlorate Reduction Pathway



Biological treatment technologies that take advantage of the mechanism shown in **[REF _Ref286664846 \h * MERGEFORMAT]** include:

- heterotrophic fixed bed (or packed bed) reactors
- fluidized bed reactors
- membrane biofilm reactors
- autotrophic hydrogen reactors
- continuously-stirred tank reactors
- *in situ* permeable biological barrier
- *in situ* electron donor delivery
- phytoremediation.

The most promising designs for biological treatment of perchlorate at drinking water facilities are those that operate either in a fixed bed or fluidized bed configuration. The California Department of Public Health (CDPH) also has identified membrane biofilm reactors as a "promising" technology for perchlorate treatment (Meyer, 2012). The first approved, full-scale membrane biofilm system for nitrate removal began operation in California in 2011 (Friese et al., 2013). Full-scale experience with the technology for perchlorate treatment, however, is limited. The literature indicates that *in situ* and other technologies are not currently used with the intent to create potable water supplies. Therefore, the remainder of this chapter focuses on the first two technologies listed above (fixed bed and fluidized bed reactors).

Both fixed bed and fluidized bed designs involve a media bed that provides a surface on which the PRB grows. The PRB can be initially introduced to the reactor with cell cultures, or the system can rely on natural populations of PRB. Drinking water systems typically rely on natural populations. Lab studies have used a variety of media in effectively reducing perchlorate, including granular activated carbon (GAC), anthracite, sand, and plastic media. Full-scale designs for perchlorate treatment have primarily used GAC. For fixed bed reactors, influent water is typically passed under pressure through a static media bed located in a vessel. An alternative fixed bed design is to use a gravity-fed concrete basin to hold the biologically active media. Fluidized bed bioreactor designs use vessels where flow, including a recycled portion, is pumped into the reactor at high rates in an up-flow design, fluidizing the media bed and allowing for more surface area for biomass growth. **[REF _Ref286827225 \h * MERGEFORMAT]** and **[REF _Ref329773247 \h * MERGEFORMAT]** provide schematic drawings for fixed bed and fluidized bed biological treatment, respectively.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Typical Schematic Layout for Fixed Bed Biological Treatment

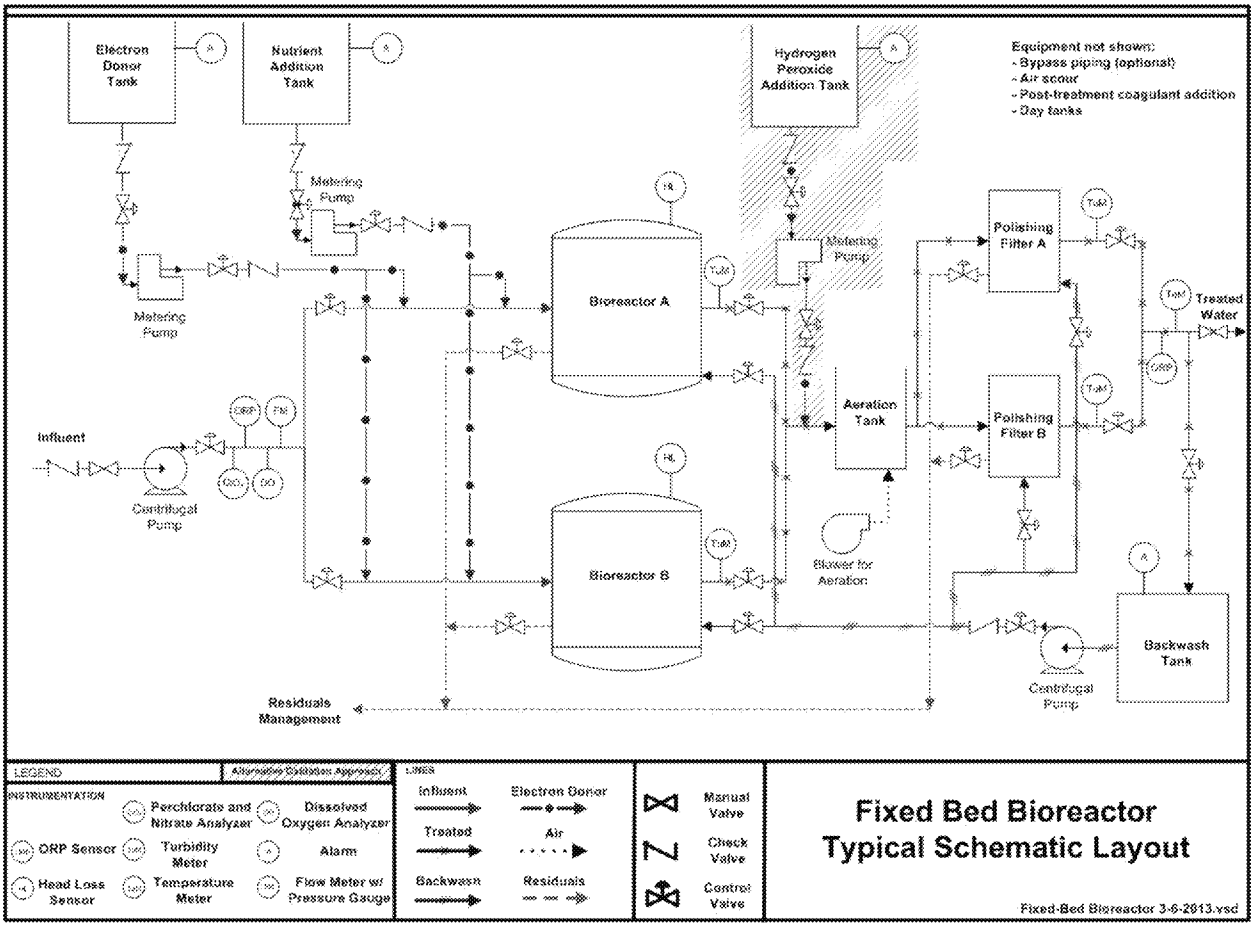
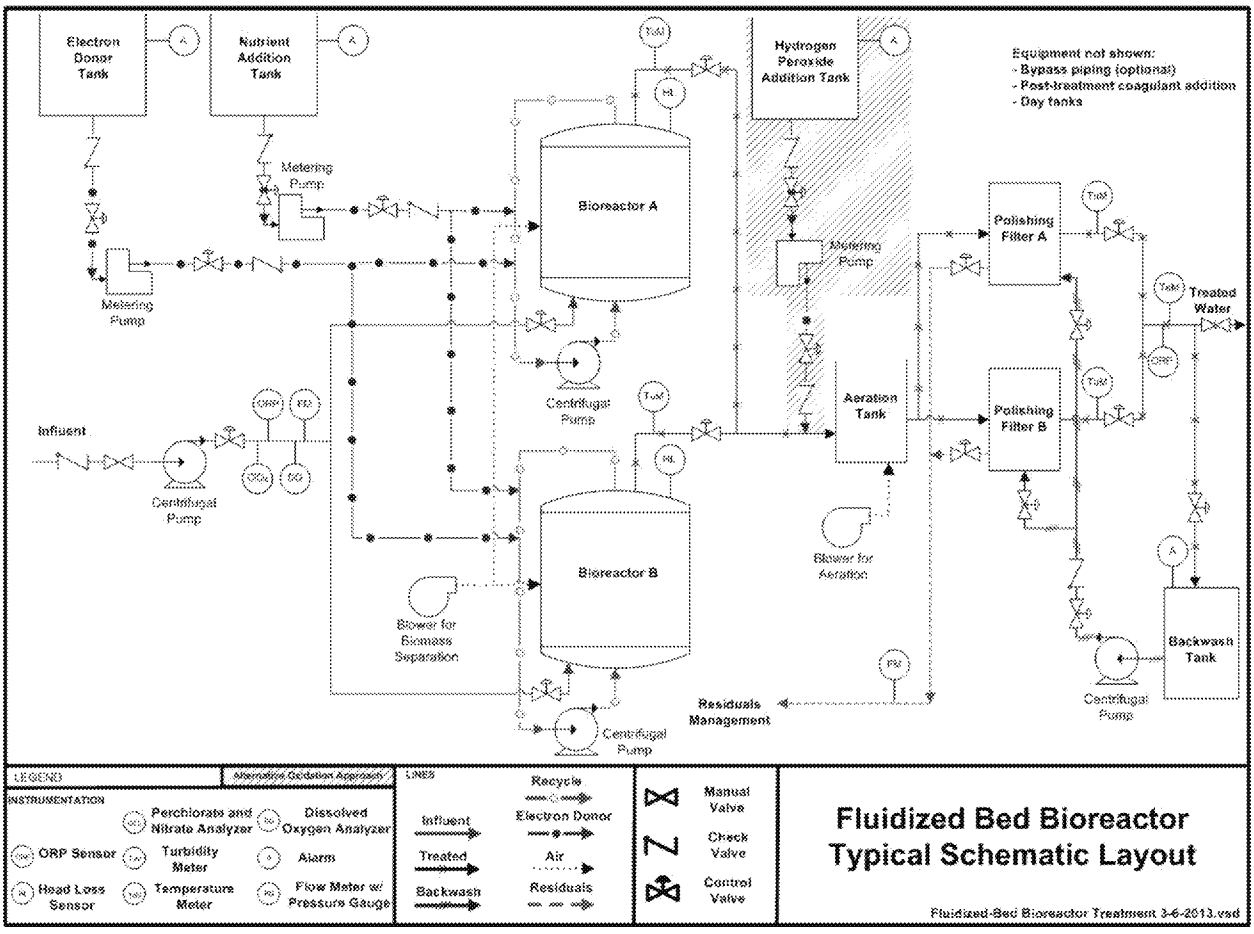


Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Typical Schematic Layout for Fluidized Bed Biological Treatment



3.2 Effectiveness for Perchlorate Removal

The State of California has identified fluidized bed biological treatment (along with ion exchange) as one of two BATs for achieving compliance with its standard for perchlorate in drinking water (California Code of Regulations, Title 22, Chapter 15, Section 64447.2). The literature contains substantial evidence of biologically-based technologies capable of reducing perchlorate to low levels in water. **[REF _Ref286666758 \h * MERGEFORMAT]** summarizes the removal efficiencies reported in the literature. It shows that fixed and fluidized bed reactors have consistently achieved removal efficiencies greater than 90 percent, reducing perchlorate to levels that are usually below detection.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Perchlorate Effectiveness Results for Biological Treatment

Removal Efficiency	Resulting Concentration (µg/L)	Study Scale and Reactor Type	Other Analytes (mg/L)	Media / Electron Donor	Data Source(s)
>92%	<4	Bench-scale fixed bed	Sulfate (0 to 220)	GAC/ Acetate or ethanol	Brown et al., 2003
>94%	<4	Bench-scale fixed bed	Nitrate (4)	Sand, plastic media / Acetic acid	Case et al., 2004; Min et al., 2004
>99%	<4	Bench-scale fixed bed	None	Sand / Acetate	Kim and Logan, 2000
>99%	<4	Bench-scale fixed bed	Nitrate (0.02), sulfate (0.04)	Celite / Acetate	Losi et al., 2002
>98%	<3	Bench-scale fixed bed	Nitrate (13), sulfate (9.3 to16.8)	GAC / Acetic acid or proprietary carbohydrate solution	Upadhyaya et al., 2015
>93%	<5	Pilot-scale fixed bed[1]	Nitrate	GAC / Acetic acid	U.S. DoD, 2008b
92% to 99%	<4	Pilot-scale fixed bed[2]	Sulfate (140 to 250), Nitrate (6 to 29), DO (4 to 8)	GAC / Acetic acid	ITRC, 2008; Brown et al., 2005
>97%	<6	Bench-scale fluidized bed	Nitrate (13), sulfate (9.3 to 16.8)	GAC / Acetic acid or proprietary carbohydrate solution	Upadhyaya et al., 2015
>99%	220 to 280	Bench-scale fluidized bed	Nitrate (15.4), sulfate (12.5)	GAC / Acetate or proprietary glycerol solution	Kotlarz et al., 2016
>99%	<5	Bench-scale fluidized bed	Nitrate, metals, volatile organics	GAC / Acetic acid	Polk et al., 2001
>99%	<2	Bench-scale fluidized bed	Sulfate (5 to 10)	GAC, sand / Ethanol, methanol, or mix	Greene and Pitre, 2000
92 to 98%	<4	Pilot-scale fluidized bed[3]	Various	GAC / Ethanol	Harding ESE, 2001; Gilbert et al., 2001
>99%	<0.5	Pilot-scale fluidized bed[4]	Various	GAC / Acetic acid	U.S. DoD, 2009; Webster and Crowley, 2010; Webster and Crowley, 2016; Webster and Litchfield, 2017
>99%	350 to <4	Full-scale fluidized bed[5]	Nitrate (1.9), sulfate (300)	GAC / Acetic acid, ethanol	Polk et al., 2001
>99%	<4	Full-scale fluidized bed[6]	Not reported	GAC / Ethanol	Greene and Pitre, 2000

Notes:

1. Ten-month field test at Rialto Well #2 site in Rialto, California treating an average of 20.2 gpm
2. Six-month field test in Santa Clarita, California treating up to 4.5 gpm
3. Eight-month field test in Rancho Cordova, California, supplying water for potable use with a design flow of 1,800 gpm
4. Field test at Rialto Well #2 site in Rialto, California treating an average of 50 gpm
5. Facility at Longhorn Army Ammunition Plant in Karnak, Texas operating at 50 gpm
6. Aerojet facility in Rancho Cordova, California operating at 3,500 gpm

The two full-scale systems identified in **[REF _Ref286666758 \h * MERGEFORMAT]** are perchlorate remediation projects. Treated water from these facilities is not used as drinking water. One of the pilot-scale studies in **[REF _Ref286666758 \h * MERGEFORMAT]**, however, was an eight-month field test that supplied potable water to local water companies (Harding ESE, 2001; Gilbert et al., 2001). Furthermore, the success of the demonstration studies in Rialto led to the design and installation of a full-scale fluidized bed system supplying drinking water to the West Valley Water District and the City of Rialto (Webster and Crowley, 2010; Webster and Crowley, 2016; Webster and Litchfield, 2017). Section [REF _Ref292953558 \r \h] provides additional details regarding the two systems designed to produce municipal drinking water (the permanent full-scale Rialto and West Valley facility and the Aerojet demonstration). Section [REF _Ref292953621 \r \h] discusses several other large-scale treatment systems.

3.2.1 Biological Treatment for Municipal Drinking Water Supply

Rialto Well #6 and West Valley Well #11, Rialto, California. As a result of the successful full-scale demonstration at Rialto Well #2 (see Section [REF _Ref292953621 \r \h]), Envirogen installed a full-scale fluidized bed treatment system designed to supply drinking water from two other nearby wells to West Valley Water District and the City of Rialto. The system is sited on a former landfill and initially designed to treat 3 million gallons per day (MGD), with an ultimate capacity of 6 MGD so that water from additional wells might be treated in the future.

Envirogen completed construction in 2013 and the system underwent extensive testing before receiving its operating permit and beginning to produce drinking water in 2016. The system includes two 14-foot diameter, 24-foot tall bioreactor vessels followed by two 12-foot diameter, 24-foot tall aeration vessels. The bioreactors include a unique system of biomass separators at the surface of the vessels. The separators remove excess biomass that detaches from the media with air scour and agitation.

Additional post-treatment includes two multimedia filters with a dissolved air floatation system for removing solids from filter backwash, followed by chlorination. This additional post-treatment is designed to replicate the surface water treatment process that West Valley Water District operates at another location and satisfy the permit requirement that the biological treatment system meet the Enhanced Surface Water Treatment rule. The permit requirements also include instrumentation and controls (chlorine, pH, nitrate, sulfide, total organic carbon, and turbidity) to monitor performance (Webster and Crowley, 2016; Webster and Litchfield, 2017).

Aerojet Field Test, Rancho Cordova, California. Aerojet conducted an eight-month field test at its facility in Rancho Cordova, California (where the company also operates the full-scale fluidized bed-based system described in [REF _Ref292953621 \r \h]) of a treatment system that included a fluidized bed biological reactor. The system removed perchlorate, nitrate, volatile organic compounds (VOCs), NDMA, and 1,4-dioxane from contaminated groundwater and supplied the treated water to local water companies for potable use (Harding ESE, 2001).

In addition to the fluidized bed reactor (designed to remove perchlorate and nitrate), the other components of the system were a multimedia filter (to remove biomass and GAC fines), an air stripper (for VOC removal), ultraviolet light/chemical oxidation (for other contaminant removal), liquid phase GAC adsorption (for other contaminant removal), disinfection (for potable water supply requirements), and clarification (for filter backwash) (Harding ESE, 2001).

The bioreactor component of the treatment system targeted perchlorate and nitrate. The total design flow rate of the fluidized bed reactor used during the field study was 1,800 gpm, which was the flow rate required to maintain the required fluidization of the GAC media. Bioreactor forward flow was variable depending on the desired recycle rate. For example, a forward flow rate of 1,200 gpm results in a recycle rate of 600 gpm (Harding ESE, 2001). To control fluidized bed level, a biofilm control system sheared excess biomass from the GAC and discharged cleaned GAC and biomass back into the reactor.

A panel of treatment experts convened by Aerojet to review results from the study concluded the following about the performance of the Aerojet Baldwin Park Operable Unit (BPOU) system (Gilbert et al., 2001):

- This combination of treatment processes removed all target chemicals below regulatory standards needed to meet potable water requirements.
- Each of the treatment processes met desired removal efficiencies in a reliable manner.
- The overall process was stable when the optimum ethanol dosage was maintained.

Investigators sampled water quality throughout the post-treatment process to evaluate the fate of excess biomass leaving the bioreactor. Specifically, they examined assimilable organic carbon, biodegradable dissolved organic carbon, and heterotrophic plate counts. Based on these analyses, they concluded that bacterial re-growth in the water distribution system would not be significant. The expert panel noted, however, that researchers did not solve the problem of cleaning excessive biomass from the GAC media. The episodic nature of the current cleaning process created problems of excessive biosolids loading on the subsequent filter that impacted water quality (Gilbert et al., 2001).

3.2.2 Other Large-Scale Biological Treatment Systems

Rialto Well #2, Rialto, California. Basin Water Inc. and Carollo Engineers Inc. both installed bioreactors as part of a perchlorate treatability field study Rialto, California. These reactors treated water from Well #2, which had been abandoned because of perchlorate contamination (Webster and Litchfield, 2017). Carollo Engineers installed and operated two parallel fixed-bed bioreactors for nitrate and perchlorate removal in a study, conducted over a 10 month period starting in February 2007, with the goal of producing treated water that met all drinking water standards. The treatment process consisted of parallel packed bed bioreactors with a 2 foot diameter and 4.7 foot bed-depth, followed by hydrogen peroxide dosing and biofiltration. The final step of the treatment process included chlorine disinfection. The bioreactor was subjected to various perchlorate spiking tests and consistently was able to treat to below detection limits for perchlorate for spiking concentrations up to 930 µg/L. The study showed that fixed-bed reactors, in combination with post-treatment processes, are a cost-effective way to produce potable water with perchlorate concentrations below detectable levels (U.S. DoD, 2008b).

Basin Water installed a full-size fluidized bed bioreactor at the same Rialto well location and tested the reactor under various operating conditions between 2007 and 2008. The purpose of the study was to test and validate the following items as they pertain to drinking water treatment (U.S. DoD, 2009; Webster and Crowley, 2010; Webster and Litchfield, 2017):

- *ex situ* bioremediation of nitrate and low concentrations of perchlorate though a fluidized bed reactor
- the short-term and long-term performance effects in allowing the system to be self-inoculated with incoming groundwater versus manually inoculating with a non-pathogenic microbial consortium
- short-term performance effects in the simulation of both a feed pump failure and an electrical shutdown
- the use of a post aeration vessel, multimedia filter, and GAC to produce to produce potable-like effluent water stream
- operational effectiveness of on-line nitrate and perchlorate analyzer systems
- long-term monitoring of system robustness and performance under steady-state and spiking perchlorate concentrations.

The Basin Water field study utilized acetic acid as the electron donor for a single fluidized bed reactor. The average flow rate into the reactor was 50 gpm. In steady-state operation, the system consistently treated perchlorate to less than 0.5 µg/L at varying influent concentrations and flow rates (Webster and Litchfield, 2017). Spiking studies showed that the maximum perchlorate concentration that could be consistently treated through the fluidized bed at a flow rate of 25 gpm was 4,000 µg/L of perchlorate, with 99.65 percent removal. The study also examined various system shut-down scenarios and proved that the fluidized bed reactor, in combination with other post-treatment processes, could treat perchlorate-contaminated groundwater to meet drinking water quality standards. The fluidized bed reactor system was able to effectively clean biosolids and maintain a consistent fluidized bed height, though the process was not described in detail (U.S. DoD, 2009). Operating costs were demonstrated to be $125 to $150 per acre foot treated. The success of the study led to the design and installation of the full-scale system producing drinking water from Rialto Well #6 and West Valley Well #11 (see Section [REF _Ref491163681 \r \h]) (Webster and Crowley, 2010; Webster and Litchfield, 2017).

Aerojet Facility, Rancho Cordova, California. Aerojet installed four fluidized bed reactors with GAC media designed and supplied by Envirogen, Inc. Envirogen designed the system to treat up to 8 mg/L of perchlorate with a loading rate of 44 pounds per day per 1,000 cubic feet of reactor volume. Each reactor has a design capacity of 1,800 gpm. Since its installation in 1998, Aerojet has operated this system at about 3,500 gpm (less than 900 gpm per reactor), treating concentrations of about 3,500 µg/L perchlorate to non-detect levels (less than 4 µg/L). Aerojet uses ethanol as the electron donor, and they re-inject the treated water into an underlying aquifer. Envirogen selected GAC media (versus sand) on the basis of pilot-testing results (Greene and Pitre, 2000).

Longhorn Army Ammunitions Plant, Karnack, Texas. U.S. Filter/Envirex and Envirogen developed and supplied a full-scale 50 gpm fluidized bed reactor with GAC media and acetic acid/nutrients addition to treat perchlorate-contaminated groundwater. After start up and acclimation, the system treats perchlorate concentrations of up to 35 mg/L (16.5 mg/L on average), reducing them to at least the target goal of 350 µg/L, and routinely to below the 5 µg/L analytical reporting limit. The system discharges treated water to a nearby stream (Polk et al., 2001).

Kerr-McGee and Pepcon Facilities, Henderson, Nevada. Full-scale fluidized bed reactors were installed to remove perchlorate at these two nearby remediation sites. The system at the Kerr-McGee site began operation in 2004, replacing ion exchange systems, and was expanded in 2006 to remove approximately 3,000 pounds per day of perchlorate from groundwater. The system at the Pepcon site began operation in 2012, replacing an *in-situ* bioremediation system. It is designed to remove approximately 1,000 pounds per day of perchlorate (Roefer, 2013).

3.3 Raw Water Quality Considerations

As shown in **[REF _Ref286666758 \h * MERGEFORMAT]**, biological treatment remains effective even in the presence of certain co-occurring contaminants. Nitrate and sulfate were present in nearly all of the studies and did not appear to interfere with the removal efficiency of the process. Biological treatment also has been shown effective in the presence of metals, volatile organic compounds, and other contaminants including NDMA and 1,4-dioxane (Polk et al., 2001; U.S. DoD, 2000; Harding ESE, 2001).

Nevertheless, raw water quality plays a role in the design of a biological treatment system. In identifying design criteria for use in full-scale treatment plant designs, the Harding ESE (2001) authors included expected raw water dissolved oxygen, nitrate, perchlorate, and total phosphorous concentrations as necessary considerations, along with water temperature. In particular, temperature plays an important role in determining the rate of biomass growth. Electron donor dose requirements increase with decreasing temperature. At temperatures below 10 degrees C, biomass growth is inhibited and bioremediation becomes unfeasible (Dugan et al., 2009; Dugan, 2010a; Dugan, 2010b).

In addition, bacteria in bioreactors require macro- and micro-nutrients in order to grow and effectively reduce perchlorate. Thus, concentrations of these nutrients in the raw water are a consideration in bioreactor effectiveness. Macro-nutrients include phosphorous and nitrogen, and necessary micro-nutrients include sulfur and iron. While source water typically contains sufficient micro-nutrients, it often has insufficient amounts of phosphorous or nitrogen to allow for bacterial growth. As a result, some full-scale designs have required supplemental addition of one or both of these nutrients (Harding ESE, 2001; U.S. DoD, 2008b; U.S. DoD, 2009).

3.4 Pre- and Post-Treatment Needs

Although the literature did not contain any studies that examine pre-treatment of source waters prior to biological treatment, certain groundwater conditions require pre-conditioning. For example, acidic ground water is not compatible with either robust microbial growth or common metallic system construction materials. In such cases, operators must raise the pH level prior to treatment. Consequently, some carbonates, sulfides, and oxides less soluble at neutral a pH might precipitate out and require filtration.

To produce drinking water from an impacted source, some form of multi-barrier system, beginning with biological treatment, may be necessary. For example, the treatment train used at the Aerojet BPOU to create potable water consists of seven different unit processes, as described in Section [REF _Ref286737077 \r \h]. Furthermore, biological treatment itself results in the production of soluble microbial organic products that become part of the treated water. Some of this material is biodegradable, and the microorganisms (at least in the case of perchlorate and

nitrate reduction) tend to be the normal soil bacteria that are involved in the natural nitrogen cycle and common in all agricultural soils (Gilbert et al., 2001). In addition, the biological treatment process also depletes the levels of oxygen in the treated water. Therefore, post-treatment will typically be required for production of drinking water. Typical post-treatment processes include (Harding ESE, 2001; U.S. DoD, 2008b; Dordelmann, 2009; Webster and Crowley, 2016; Webster and Litchfield, 2017):

- reoxygenation or aeration for saturation with oxygen, using hydrogen peroxide addition or an aeration tank
- a polishing filter (using GAC or mixed media) for removal of turbidity, sulfide, and/or dissolved organic content, possibly including coagulant addition before filtration
- disinfection via ultraviolet light or chlorination.

3.5 Waste Generation and Residuals Management Needs

Because biological treatment offers complete destruction of the perchlorate ion, the technology does not generate a perchlorate-bearing waste stream. An active bioreactor, however, will have a continuous growth of biomass resulting from consumption of dissolved oxygen, nitrates, and perchlorate. In most bioreactor designs, excess biomass must be removed periodically. This removal results in one or more residual streams, the characteristics of which depend on the removal process used.

In fixed bed bioreactors, biomass removal typically is accomplished using a backwash process, which generates spent backwash water containing the excess biosolids (and some lost media). This backwash water is non-toxic and can typically be discharged to a local sewer. For facilities without the option of sewer disposal, a clarification and recycle process would be needed (U.S. DoD, 2008b). For fluidized bed reactors, one case study describes the use of a continuously operated separation device that uses supplied air to remove media and biomass from the top of the bed and direct it to a separation chamber. This arrangement was used in combination with an in-bed eductor to intermittently remove biomass growth from deeper in the bed. After treatment through an adsorption clarifier and multimedia filter, the study reports that the remaining residuals were "dilute enough that no special handling or pretreatment requirements should be necessary for most/all publicly-owned treatment works (POTWs) to accept" (U.S. DoD, 2009).

Downstream polishing through filtration (see Section [REF _Ref286739214 \r \h]), when used as post-treatment, can also generate residual wastes in the form of backwash water and separated solids. The authors of the Harding ESE (2001) report suggest that clarifier solids could be discharged directly to sewer or filter pressed to reduce volume prior to ultimate disposal. The full-scale drinking water treatment facility in Rialto uses dissolved air floatation, followed by a sludge press, to treat backwash from post-treatment filtration (Webster and Litchfield, 2017). Backwash water from downstream polishing would be expected to have characteristics similar to water from direct backwash of a fixed bed reactor.

In addition, biological treatment can itself be a treatment technology for residuals from other perchlorate removal technologies, such as spent ion exchange regenerant or membrane reject. Appendix A discusses this use of biological treatment.

3.6 Critical Design Parameters

Critical design parameters for biological treatment systems removing perchlorate are:

- Support media type
- EBCT or hydraulic residence time (HRT)
- Bed expansion (for fluidized bed reactors)
- Electron donor type and dosage
- Nutrient addition
- Backwash and biomass separation design
- Recycle rate (for fluidized bed reactors)
- Post-treatment requirements.

The paragraphs below discuss each of these parameters in more detail. As noted in Section [REF _Ref286743169 \r \h], fixed bed and fluidized bed reactors are the most promising approaches for drinking water treatment. Therefore, this section focuses on design parameters specific to these two types of biological treatment system. Three of the full-scale studies (Harding ESE, 2001; U.S. DoD, 2008b; U.S. DoD, 2009) identified critical design criteria for these types of reactors and were instrumental in guiding the discussion here. This section provides a general discussion of the design parameters and the range of values reported in the literature for these parameters. Chapter [REF _Ref326047741 \r \h] identifies the specific values for each parameter used in EPA's cost estimates.

Support Media Type

As discussed in Section [REF _Ref286743169 \r \h], in both fixed and fluidized bed reactors, PRB require a media surface on which to grow. As shown in **[REF _Ref286666758 \h * MERGEFORMAT]**, studies have used a variety of media in effectively reducing perchlorate, including GAC, anthracite, sand, and plastic media. Full-scale designs for perchlorate treatment, however, have primarily used GAC (Harding ESE, 2001; Greene and Pitre, 2000; Polk et al., 2001; U.S. DoD, 2008b; U.S. DoD, 2009).

Empty Bed Contact Time or Hydraulic Residence Time

EBCT is defined as the volume of support media divided by the flow rate. Minimum EBCT needed in order for perchlorate to be fully reduced is the primary design parameter in sizing fixed bed bioreactor vessels. For fluidized bed bioreactors, HRT is the more accurate term for the primary design parameter. HRT is the time required for treated water to move through the fluidized media bed. For larger flows, multiple bioreactors will be operated in parallel. Typical full-scale bioreactor designs have an EBCT or HRT in the range of 10 to 12 minutes for both fixed bed (U.S. DoD, 2008b) and fluidized bed reactors (Harding ESE, 2001).

Bed Expansion

For fluidized bed bioreactors, an additional important vessel sizing consideration is bed expansion. Target bed expansions are used to determine the height of the vessels. Peer review of EPA's biological treatment cost model (see Chapter [REF _Ref326047741 \r \h]) provided information on typical bed expansion values. Typically, the vessel is filled with a fixed bed depth of media and initially fluidized to 40 to 50 percent. As the biomass grows, the fluidized media bed expands to 70 percent of the initial fixed bed depth. Biomass separation maintains expansion

at this target level. Additional space at the top of the vessel provides a safety factor to prevent fluidized media from exiting the reactor.

Electron Donor Type and Dosage

As discussed above, bioreactor designs require the presence of an electron donor (or substrate) for the reduction of perchlorate. For fixed bed bioreactors, electron donors are injected into the influent water prior to entering the bioreactor. In fluidized bed bioreactors, injection typically occurs in the recycle stream. As shown in **[REF _Ref286666758 \h * MERGEFORMAT]**, a wide variety of electron donors have been tested, including acetate, acetic acid, lactate, ethanol, methanol, carbohydrate by-product, hydrogen, propane, and proprietary glycerol- or carbohydrate-based solutions. Full-scale designs for perchlorate treatment, however, have typically used acetic acid or ethanol (Harding ESE, 2001; U.S. DoD, 2008b; U.S. DoD, 2009; Greene and Pitre, 2000; Polk et al., 2001).

Determining the correct electron donor dose is critical in the effectiveness of perchlorate reduction in the bioreactor. Since oxygen and nitrates will be reduced prior to perchlorate reduction, the electron donor dose must be large enough to fully reduce all three. However, the dose cannot be too large or sulfides might form and be present in the effluent along with excess organic carbon, requiring additional post-treatment (Harding ESE, 2001).

Electron donor dose is dependent on site-specific conditions, including raw water characteristics. Therefore, determining the dose requirements for the electron donor typically requires pilot study tests, along with stoichiometric and thermodynamic calculations. The following site-specific relationships were developed for two full-scale treatment designs using ethanol and acetic acid:

$$C_e = 0.903\ O_2 + 2.229\ NO_s^-\text{-}N + 0.581\ ClO_4^-$$

(Harding ESE, 2001)

$$C_{aa} = O_2 + 2.86\ NO_s^-\text{-}N + 0.64\ ClO_4^-$$

(U.S. DoD, 2008b)

where:
C_e = required ethanol concentration (mg/l)
C_{aa} = required acetic acid concentration (mg/l)
NO_3-N = influent nitrate-nitrogen concentration (mg/l)
O_2 = influent DO concentration (mg/l)
ClO_4^- = influent perchlorate concentration (mg/l)

As can be seen in these stoichiometric equations, influent concentrations of oxygen, nitrate-nitrogen, and perchlorate need to be available to determine the electron dose. Tests have proven that the electron donor dose is dependent on temperature and that decreasing the water temperature will result in an increase in necessary electron donor dose. However, these small changes are in the range of 3 percent change of dose for a 5 degrees C change (Harding ESE, 2001).

Nutrient Addition

As discussed in Section [REF _Ref286744617 \r \h], bacteria in bioreactors require nutrients. Although these nutrients are sometimes present in source water, full-scale designs have required addition of macro-nutrient such as nitrogen and/or phosphorous. While there are a number of methods for adding nitrogen and phosphorous to the influent, the typical options are addition of ammonium chloride for supplemental nitrogen addition and/or addition of phosphoric acid for supplemental phosphorous (Harding ESE, 2001; U.S. DoD, 2008b).

Backwash and Biomass Separation Design

As discussed in Section [REF _Ref286744911 \r \h * MERGEFORMAT], bioreactors require periodic removal of accumulated biomass. Removal of the biomass is achieved in different ways depending on the bioreactor design type. For fixed bed bioreactors, an air scour is used followed by water flush to remove biomass from the media. A backwash basin and pump is needed to supply the water for backwashing. This backwash design is similar to that used in other treatment technologies, such as GAC and greensand filtration. Typical fixed bed bioreactors have a backwash interval in the range of 17 to 24 hours, determined based on target head across the media bed (U.S. DoD, 2008b).

For fluidized bed bioreactors, the expanded bed volume within the fluidized bed reactor will continue to expand as biomass accumulates. This expansion occurs because the specific density of the media plus biomass is less than that of the media alone. It becomes necessary to dislodge biomass growth from the media, thus increasing the specific density and decreasing the fluidized bed volume. Effective methods and equipment for biomass separation include mechanical separation of biomass using eductors or using air scour to sheer the biomass from the media. The amount of air required for biomass separation is around 0.3 cubic feet per hour per gpm of treated water (U.S. DoD, 2009).

Recycle Rate

Designs of fluidized bed reactors use high pumping rates to keep the media in the bioreactor fluidized. A recycle stream is typically used to provide enough water to satisfy these pumping rates. Since feed pumping rates also determine the expansion height of the media bed, the recycle rate must be limited so that the feed pumping rate doesn't expand the fluidized media past the target height. A typical recycle rate, based on peer review comments on EPA's biological treatment cost model (see Chapter [REF _Ref326047741 \r \h]), is 50 percent.

Post-treatment Requirements

Section [REF _Ref350938612 \r \h] identifies post-treatment processes typically required for biological treatment, which can include reoxygenation, filtration, and disinfection.

4 Membrane Technologies

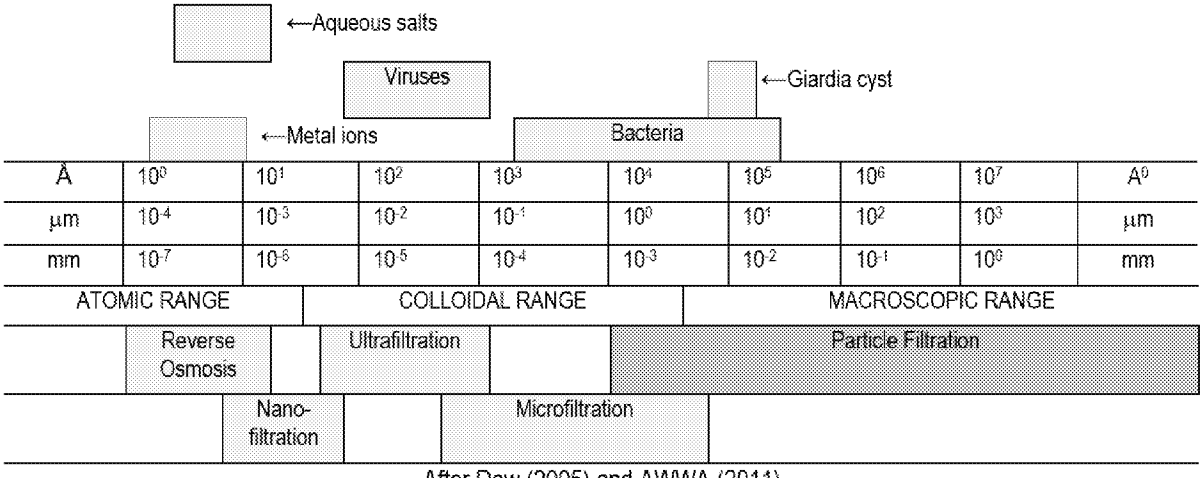
4.1 Operating Principle

Membrane filtration processes physically remove perchlorate ions from drinking water. This technique does not destroy the perchlorate ion and, therefore, creates a subsequent need for disposal or treatment of perchlorate-contaminated waste. Membrane filtration technologies evaluated for perchlorate treatment include reverse osmosis (RO), nanofiltration (NF), and ultrafiltration (UF).

These processes separate a solute such as perchlorate ions from a solution by forcing the solvent to flow through a membrane at pressure. RO depends on applying high pressures across the membrane in the range of roughly 100 to 1,000 pounds per square inch gauge (psig) in order to overcome the osmotic pressure differential between the saline feed and product waters. The NF process uses pressures in the range of 75 to 150 psig, while pressures for UF typically range from 3 to 40 psig (USEPA, 2003).

In all three processes, the membrane is semi-permeable, transporting different molecular species at different rates. Water and low-molecular weight solutes pass through the membrane and are removed as permeate, or filtrate. Dissolved and suspended solids are rejected by the membrane. Along with a portion of the feed water, these solids are removed as concentrate, or reject. The size range of the rejected solids varies by the type of membrane used, as shown in **[REF _Ref329764419 \h * MERGEFORMAT]**.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Particle Sizes and Membrane Process Ranges



After Dow (2005) and AWWA (2011)

Membranes may remove ions from feed water by a sieving action (called steric exclusion), or by electrostatic repulsion of ions from the charged membrane surface. RO membranes, which have an effective pore size of 0.001 microns or less, primarily remove perchlorate by the steric mechanism. UF membranes, with a pore size of roughly 0.01 to 0.1 microns, remove perchlorate primarily by electrostatic repulsion. NF membranes have effective pore sizes of roughly 0.001 to 0.01 microns. Various NF membranes may operate by both mechanisms to varying degrees

(Yoon et al., 2004; USEPA, 2005; Nam et al., 2005; Yoon et al., 2005a; Yoon et al., 2005b; Amy et al., 2006).

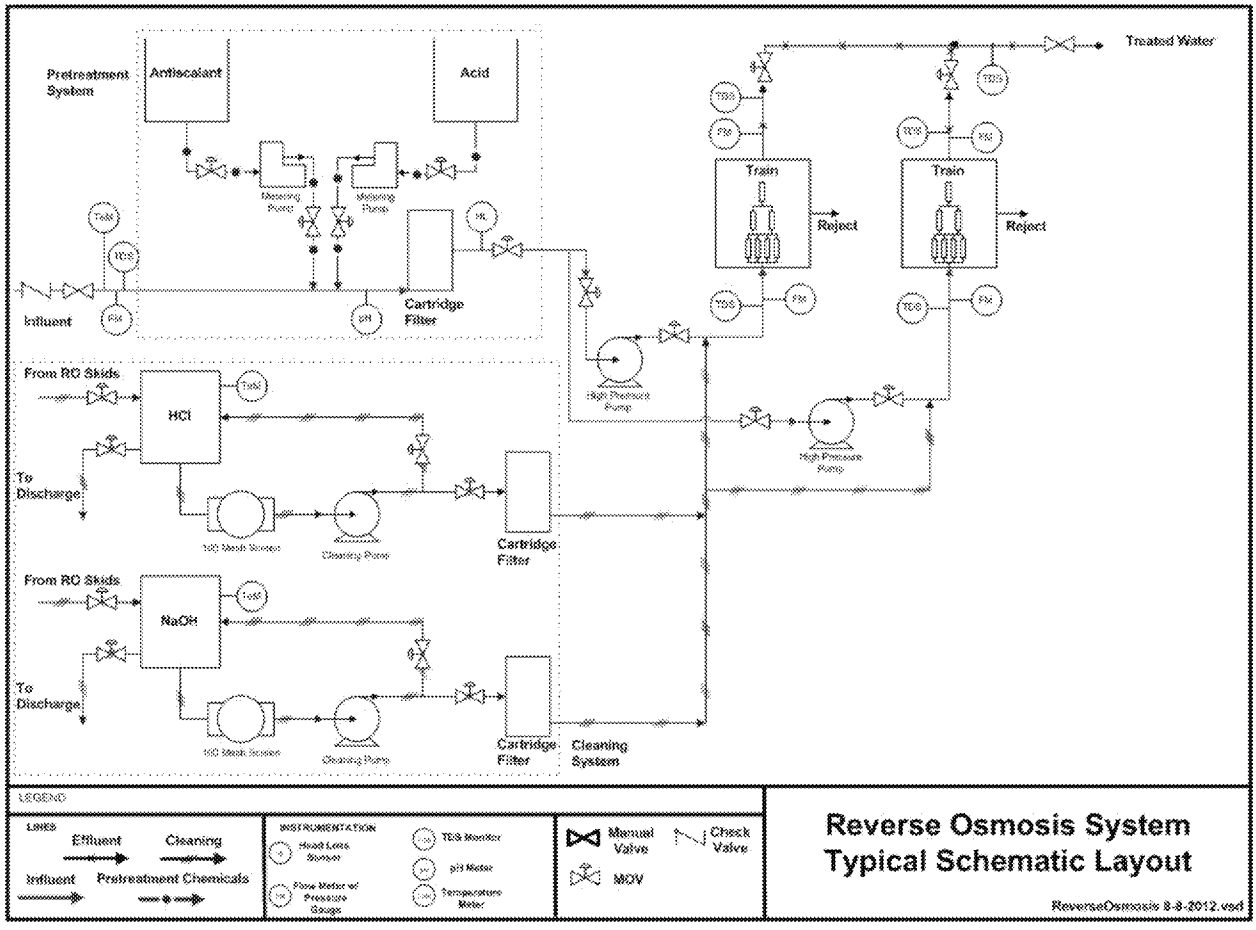
As discussed below in Section [REF _Ref329764874 \r \h], of the membrane processes, RO has shown the most promise for removing perchlorate. Therefore, this chapter focuses primarily on the technical details of the RO treatment process. It discusses UF and NF mainly in terms of the available data on their effectiveness, with less discussion of their operating principle and relevant design parameters. Note, however, that practical operation of an NF system is very similar to that of an RO system.

For municipal drinking water treatment, RO membranes are most often used in a spiral-wound configuration. A spiral wound membrane consists of several membrane envelopes, layered with feed spacers and rolled together in a spiral around a central permeate collection tube. Each envelope consists of a flat membrane sheet folded in half over a porous membrane permeate carrier, and glued on the remaining three sides to completely enclose the carrier. The envelopes are connected to a central permeate collection tube. After the envelopes and feed spacers are rolled around the tube, the assembly is enclosed in a shell to form a membrane element. Different RO elements are manufactured for different scenarios, including seawater desalination (seawater RO), treatment of brackish water with dissolved solids roughly in the range of thousands of mg/L (brackish water RO), and treatment of less saline water (low-pressure RO). Elements that are intended for higher feed salinity have smaller effective pore sizes. They therefore offer higher rejection of dissolved ions, and require higher pressures for operation.

Multiple RO or NF elements are placed within a pressure vessel. To achieve the target removal efficiency and water recovery, these pressure vessels often are arranged in sequential stages, typically up to three depending on the recovery to be achieved (AWWA/ASCE, 2005; Dow, 2005). When multiple stages are used, the number of pressure vessels decreases from stage to stage. Permeate or finished water is collected from each pressure vessel. The concentrate from the first membrane stage serves as the feed to the second and the concentrate from the second stage serves as the feed to the third. Consequently, each successive stage of the process increases the total system recovery (Jacangelo et al., 1998). As the feed water travels through the membrane system and becomes more concentrated, its osmotic pressure increases. The feed pressure must overcome this osmotic pressure. The final concentration in the concentrate water therefore has a major effect on the required feed pressure and energy use.

The membrane stages in combination make up an RO treatment train. A treatment system may have multiple trains. **[REF _Ref286827747 \h * MERGEFORMAT]** provides a schematic drawing for an RO treatment facility; each rectangular box within a train represents a pressure vessel that contains multiple membrane elements. An NF treatment facility would be nearly identical, with the primary difference being the type of membranes used and the operating pressures.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Typical Schematic Layout for a Reverse Osmosis (or Nanofiltration) Treatment Facility



4.2 Effectiveness for Perchlorate Removal

Although the literature pertaining to perchlorate removal using membrane technologies is limited, pilot and bench-scale studies have demonstrated that perchlorate can be substantially removed by RO. The studies also demonstrate widely varying removal of perchlorate with NF and UF processes, and have investigated favorable conditions for its removal (Liang et al., 1998; Yoon et al., 2002; Yoon et al., 2003; Yoon et al., 2004; Nam et al., 2005; Yoon et al., 2005a; Yoon et al., 2005b; Sanyal et al., 2015). There is no large-scale demonstration study of membrane use for perchlorate removal.

Pilot-scale treatability work at the Metropolitan Water District of Southern California showed that NF and RO membranes consistently removed greater than 80 percent of the perchlorate (up to 98 percent for RO and 92 percent for NF) depending on influent concentration (Liang et al., 1998). Recycling 50 percent of the concentrate had no effect on overall perchlorate rejection. **[REF _Ref286757715 \h * MERGEFORMAT]** summarizes effectiveness results for this pilot-scale work, along with results from additional, smaller scale bench studies.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Perchlorate Effectiveness Results for Membranes

Technology/Source	Removal Efficiency	Raw Water Concentration	Location and Source Water	Study Scale
RO and NF (Liang et al., 1998)	RO up to 98% NF up to 92%	20 to 2,000 µg/L (some trials used perchlorate-spiked source water)	Metropolitan Water District of Southern California, La Verne Treatment Plant, CA; Pretreated Colorado River Water	Pilot study (12 gpm)
Surfactant modified UF (Yoon et al., 2003)	Up to 80%	100 µg/L (perchlorate-spiked)	Synthetic water and a blend of Colorado River Water and State Project Water from the Metropolitan Water District, CA	Bench study (225 milliliters per minute)
NF and UF (Yoon et al., 2002)	Up to 75%	100 µg/L (perchlorate-spiked)	Synthetic water with pure component perchlorate, also combined with other salts	Bench study (no flow given)
NF and UF (Yoon et al., 2004)	NF up to 80% (natural water) or 89% (synthetic water) UF up to 5% (natural water) or 66% (synthetic water)	100 µg/L (perchlorate-spiked)	Synthetic water and Colorado River Water from the Metropolitan Water District, CA, spiked with perchlorate	Bench study (100 to 225 milliliters per minute)
RO and NF (Nam et al., 2005)	RO up to 95% NF up to 70%	100 µg/L (perchlorate-spiked)	Ground waters from the Castaic Lake Water Agency, CA	Bench study (no flow given)
RO (USEPA, 2005)	From 125–2,000 µg/L to 5–80 µg/L	125 to 2,000 µg/L	Unspecified perchlorate-contaminated ground water	Bench study (no flow given)
RO and NF (Yoon et al., 2005a)	RO up to 95% NF up to 55%	100 µg/L (perchlorate-spiked)	Blend of Colorado River Water and State Project Water from the Metropolitan Water District, CA, spiked with perchlorate	Bench study (20 milliliters per minute)
RO, NF, and UF (Yoon et al., 2005b)	RO up to 95% NF up to 78% UF up to 29%	100 µg/L (perchlorate-spiked)	Synthetic water	Bench study (no flow given)
RO, NF, and surface modified NF (Sanyal et al., 2015)	RO up to 95.8% NF up to 70.1% Surface modified NF up to 93%	10,000 µg/L (perchlorate-spiked)	Perchlorate-spiked deionized water	Bench study (0.26 gpm)

Bench-scale studies show the effects of steric/size exclusion and electrostatic exclusion on perchlorate transport through membranes to varying degrees. RO, while removing perchlorate,

also removes most other salts, requires high operating pressures, and is prone to significant flux decline. Membrane processes that operate at lower pressures, such as NF or UF, may be effective for perchlorate removal through selectivity based on size and/or charge. However, bench studies show significant variability in these membranes' ability to remove perchlorate, depending on other constituents of the source water. See Section [REF _Ref292709479 \r \h] for further discussion. One bench study modified commercial NF membranes using layer-by-layer surface deposition of polyelectrolytes. This study showed that the modified NF membranes could achieve perchlorate removal nearly equal to that of RO membranes. The study, however, did not examine the effect of differing source water quality on the membranes and research on the modified membranes does not yet appear to have progressed beyond the lab (Sanyal et al., 2015).

4.3 Raw Water Quality Considerations

High levels of alkaline earth cations (Ca^{2+} or Mg^{2+}) can cause membrane scaling (Yoon et al., 2003), leading to a decline in product water flux. One study showed that calcium carbonate scaling was also associated with a decline in perchlorate rejection, likely because the scale reduced the surface charge of the membrane (Yoon et al., 2005b). Other substances, such as silica, may also cause flux decline; however, there are no studies of the resulting effect on perchlorate rejection.

Membrane fouling may be reduced either by reducing the pH of the feed water or by adding an antiscalant chemical. However, for membranes that reject perchlorate electrostatically (primarily NF and UF membranes), studies of several synthetic waters show that a reduced feed pH reduces the rejection of perchlorate (Yoon et al., 2004; Yoon et al., 2005a; Yoon et al., 2005b). The lower pH has been shown to diminish the negative surface charge of the membranes, inhibiting the electrostatic rejection mechanism. One study (Yoon et al., 2005b) demonstrated that a phosphonate-based antiscalant improved both product water flux and perchlorate rejection. In these studies, perchlorate rejection by RO membranes was much less sensitive to the feed water pH.

The same studies demonstrated that a high concentration of other ions, particularly divalent cations, in the membrane feed water can reduce perchlorate rejection. Again, the studies attributed the reduced rejection to a diminished membrane surface charge. One study that included one natural water and several synthetic waters (Yoon et al., 2004) found that the natural water had worse perchlorate rejection than the most similar synthetic water for NF and UF membranes.

4.4 Pre- and Post-Treatment Needs

In general, pretreatment requirements for membrane technologies depend on influent water quality as well as the type of membrane used. RO and NF membranes are often used after media filtration, or more recently, after UF or microfiltration membranes. Membrane filtration processes often include a prescreen or cartridge filter to remove sediment that could damage the membranes. RO and NF membranes often require pH adjustment or antiscalant.

The pilot study of RO and NF membrane elements (Liang et al., 1998) included prechlorination and conventional filtration (rapid mix, flocculation, sedimentation, and filtration). Pretreatment requirements, however, typically are independent of the specific contaminant targeted for

removal. Calculations such as the silt density index (SDI), found in ASTM standard D3739-94, can provide insight into the fouling problems that are inherent in any membrane system. SDI measures the fouling potential of suspended solids. Manufacturers typically specify maximum SDIs of 3 to 5 for RO and NF elements. In addition, it is important to model and conduct pilot studies to assess the potential for fouling from substances such as calcium carbonate, silica, calcium fluoride, barium sulfate, calcium sulfate, strontium sulfate, and calcium phosphate. The Langelier saturation index (LSI), described in ASTM standard D4189-94, characterizes the potential for $CaCO_3$ scaling. The LSI is used to indicate the tendency of water to precipitate, dissolve, or be in equilibrium with calcium carbonate, and what pH change is required to bring the water back to equilibrium. The scaling potential of other substances may be determined from a saturation calculation.

Although the perchlorate literature does not address post-treatment requirements, the permeate from RO filtration is essentially deionized water, and generally requires post treatment for corrosion control before it enters a distribution system (AWWA/ASCE, 2005). In other drinking water treatment applications using groundwater, the permeate is often blended with untreated water to produce a less corrosive finished water. If the source water has a sufficiently low concentration of perchlorate and other contaminants, higher rates of blending will be possible, likely reducing post-treatment requirements.

4.5 Waste Generation and Residuals Management Needs

Membrane filtration produces a waste stream called the concentrate (or reject). This waste stream contains all removed dissolved and suspended solids, and must be further treated and/or disposed of. Membrane system designs generally set a recovery rate (i.e., the ratio of permeate to feed flow) based on the scaling potential of the resulting concentrate water. The presence of a particular target contaminant has little or no effect on the selected recovery rate. Therefore, it is likely that the concentrate flow would represent a substantial share of influent flows. In other applications, concentrate flows can account for 15 to 30 percent of influent, which implies a fairly large perchlorate-contaminated waste stream for subsequent treatment or disposal.

In general, full-scale RO systems handle concentrate using surface water discharge or discharge to sanitary sewer, with a small number using deep well injection, evaporation ponds, or spray irrigation (U.S. DoI, 2001). The large volume of residuals is a well-known obstacle to adoption of RO technology. In the case of perchlorate removal by centralized treatment plants, the high perchlorate concentration in the residuals might limit the disposal options or require additional treatment prior to disposal, depending on state and local discharge regulations. Studies of treatment of perchlorate-bearing RO residuals are limited to a few laboratory-scale studies. These include biological (Giblin et al., 2002) and thermal treatment (ARA, 2000) of RO concentrate, discussed in more detail in Appendix A.

In addition, periodic cleaning of the membrane system is necessary to recover productivity lost to fouling. This cleaning may include cycles of acid and caustic wash, depending on the nature of the fouling. Since the spent cleaning solution is generated infrequently and in small amounts, it is typically diluted by and handled with the concentrate.

4.6 Critical Design Parameters

As discussed in Section [REF _Ref329764874 \r \h], pilot and bench-scale studies have demonstrated that perchlorate can be substantially removed by RO. The studies demonstrate widely varying removal of perchlorate with NF and UF processes. Therefore, this section focuses on critical design parameters for RO. For comparison, it notes available data for NF, but does not discuss UF.

Critical design parameters for RO systems removing perchlorate are:

- Feed water quality
- Membrane type and feed water pressure
- Recovery rate
- Flux rate
- Pretreatment requirements.

[REF _Ref286758013 \h * MERGEFORMAT] shows design information from the pilot-scale work performed at the Metropolitan Water District of Southern California, La Verne Treatment Plant, which used RO and NF to remove perchlorate from pretreated Colorado River Water (Liang et al., 1998). The paragraphs below discuss each of the parameters listed above in more detail. Values for other RO design parameters (e.g., cleaning procedures, residuals discharge options), while not specifically addressed in the literature reviewed here, are well documented for RO treatment in general. EPA has no reason to expect a significant difference in these parameters for RO systems treating perchlorate. This section provides a general discussion of the design parameters and the range of values reported in the literature for these parameters. Chapter [REF _Ref326047741 \r \h] identifies the specific values for each parameter used in EPA's cost estimates.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Critical Design Parameters for Reverse Osmosis (and Nanofiltration)

Membrane Filtration Critical Design Parameter	Value from the Reference (Liang et al., 1998)
Feed water quality	TOC = 2.40 – 3.50 mg/L UV^{254} = 0.024 – 0.032 /cm Conductivity = 969 – 1030 micro-ohm/cm Temperature = 26°C pH = 8.09 – 8.24 Turbidity = 0.12 – 0.18 NTU Particle count = 113 – 1590 /milliliter
Membrane type	One membrane element, 4-inch diameter, 40 inches long, thin-film composite with negative surface charge RO 72 square foot active area, specific flux 0.14 gallons per day per square foot (gpd/ft^2 or gfd) per pound per square inch (gfd/psi) NF 82 square foot active area, specific flux 0.17 gfd/psi, molecular weight cutoff 300 Daltons
Average feed water pressure	RO 106 psig NF 87 psig
Recovery rate	No data is given.
Flux rate	15 gfd for both RO and NF
Pretreatment	The raw water was treated via prechlorination, rapid mix, flocculation, sedimentation, and filtration prior to passing through the membranes. The prechlorination dose was adjusted to maintain an effluent free-chlorine residual of 0.5 to 1.0 mg/L. The coagulation step used 5 mg/L alum and 1 mg/L poly-DAD/MAC polymer. Six column-type filters were used: four dual-media filters with 20 inches of anthracite coal and 8 inches of silica sand; and two tri-media filters with 8 inches of silica sand and 3 inches of ilmenite. The filter effluent was passed through a dechlorination unit.

Feed Water Quality

As discussed in Section [REF _Ref329766889 \r \h], feed water quality can determine pretreatment and cleaning requirements. Furthermore, as discussed below, it affects the values achievable for other relevant design parameters, such as recovery and flux rate. Finally, higher levels of total dissolved solids correspond to higher osmotic pressure in the membrane concentrate, and thus increase energy requirements. Feed water quality parameters that are crucial include temperature, pH, SDI, total dissolved solids, and concentrations of ions that can lead to the oversaturation of scaling salts, such as those listed in Section [REF _Ref329766889 \r \h].

Membrane Type and Feed Water Pressure

Membrane elements from different manufacturers, and different elements from the same manufacturer, may have widely varying water and ion permeabilities. Effective pore size and maximum feed pressure determine whether a membrane is characterized as RO or NF. As discussed in Section [REF _Ref329767986 \r \h], RO membranes have pore sizes of 0.001 microns or less and operate at pressures in the range of roughly 100 to 1,000 psig. NF membranes have pore sizes of roughly 0.001 to 0.01 microns and use pressures in the range of 75 to 150 psig. Membrane elements also are characterized by their diameter (usually 4 to 18 inches),

active area (in square feet), and specific flux rate (measured in gfd per psi of net driving pressure[9]). Other relevant operating specifications include maximum recovery in one element, minimum concentrate flow, maximum feed SDI, minimum operating pH, maximum operating temperature, and maximum pressure drop permitted in a single element and a complete pressure vessel.

[REF _Ref286758013 \h * MERGEFORMAT] shows data on the specific membranes tested for perchlorate by Liang et al. (1998). The RO membranes (which showed higher perchlorate removal efficiency than the NF membranes) operated at the low end of the typical range for that technology (106 psig).

Recovery Rate

As discussed above, RO produces a permeate flow (water with most dissolved solids removed) and a concentrate flow (residual water rejected by the membrane). The recovery rate is the percentage of the influent flow that is recovered as permeate. Increasing the recovery rate will increase the concentration of dissolved solids in the membrane reject water, and will thus increase the required feed pressure and the potential for membrane scaling. Thus, the achievable recovery rate depends on the quality of the source water as well as the pretreatment of the water (AWWA/ASCE, 2005), and systems with high levels of total dissolved solids in their feed water will typically operate at lower recovery rates than systems with lower levels.

For a given membrane and feed water, a higher recovery rate will require the use of more elements in series. The model accomplishes this by increasing the number of elements per pressure vessel and/or by increasing the number of stages in the system. For NF membrane elements, the target recovery will typically be between 80 and 90 percent. For RO elements, the target recovery will typically be between 50 and 85 percent. Although Liang et al. (1998) did not report recovery rates achieved in their pilot studies, recovery rate is driven by overall feed water quality, not the specific contaminant being targeted. Therefore, EPA has no reason to expect a significant difference in recovery rate for RO systems treating perchlorate from the values typically documented for RO systems in general.

Flux Rate

The flux of the system is the rate of permeate water per unit of membrane area, typically measured in gfd. While each stage of a membrane system will have a different flux, the average flux over all elements is a fundamental design parameter. In general, the higher the quality of the feed water, the higher the flux that may be achieved. Operating with excessively high flux, however, leads to fouling of the membrane elements. Depending on the nature of the fouling, it may be reversed by cleaning, or may require replacement of the elements.

For many ground waters, systems can operate successfully with fluxes between 16 and 20 gfd. Surface waters require lower fluxes, typically between 12 and 17 gfd, depending on the SDI of

[9] Net driving pressure is equal to the feed pressure at a particular point in the pressure vessel minus the osmotic pressure of the feed water.

the source water. Pretreatment will usually permit the use of a higher flux. The pilot studies by Liang et al. (1998) used a flux rate of 15 gfd, in the typical range for surface water.

Pretreatment Requirements

As discussed in Section [REF _Ref329766889 \r \h], to reduce fouling of the membrane, some type of pretreatment is usually required. The pilot studies by Liang et al. (1998) used extensive pretreatment, the equivalent of conventional filtration. Conventional filtration, however, would likely already be present at surface water sources that require additional treatment to remove perchlorate. The types of pretreatment that would more likely need to be added to an existing treatment train for implementation of RO include those identified in Section [REF _Ref329766889 \r \h], such as cartridge filtration and acid and/or antiscalant addition.

5 Point-of-Use Treatment

5.1 Operating Principle

A POU device uses a miniaturized version of a centralized treatment process to meet water quality standards for consumption at individual taps (e.g., a kitchen sink). When a system installs, controls (i.e., owns), and maintains POU devices at all customer locations where water is consumed (e.g., residences), it can forego centralized treatment (USEPA, 2006b). Because POU devices treat a small fraction of the water delivered by a system, a compliance program that relies on POU devices may be more cost-effective for smaller systems.

For perchlorate removal, the NSF Joint Committee on Drinking Water Treatment Units has added a protocol to *NSF/ American National Standards Institute (ANSI) Standard 58: Reverse Osmosis Drinking Water Treatment Systems* that requires an RO unit to be able to reduce perchlorate from a challenge level of 130 µg/L to a target level of 4 µg/L (NSF, 2004). Several organizations (e.g., NSF International, Underwriters Laboratories, Water Quality Association) provide third-party testing and certification that POU devices meet drinking water treatment standards. There are no perchlorate certification standards for other types of POU devices such as those using ion exchange media. Therefore, the discussion in this section focuses on POU RO devices.

The operating principle for POU RO devices is the same as centralized RO: steric exclusion and electrostatic repulsion of ions from the charged membrane surface. In addition to an RO membrane for dissolved ion removal, POU RO devices often have a sediment pre-filter and a carbon filter in front of the RO membrane, a 3- to 5-gallon treated water storage tank, and a carbon filter between the tank and the tap.

To meet a perchlorate drinking water standard, a system would need to purchase, install, and maintain certified POU RO devices for all customers. Usually, a system would install a single POU RO device at the kitchen tap for each residential customer. Nonresidential customers might require multiple devices (e.g., for drinking fountains). Installation requires retrofitting the device into existing plumbing fixtures (e.g., tapping into the water supply line to insert a treated water line with a dedicated tap and adding a wastewater connection for the RO membrane concentrate or reject). Maintenance primarily consists of filter replacement, often on a fixed schedule that varies by filter type. Monitoring water quality at individual treated water taps will also be necessary to demonstrate compliance with a perchlorate drinking water standard.

5.2 Effectiveness for Perchlorate Removal

There are no perchlorate removal case studies that use POU RO. Nevertheless, bench-scale and pilot testing indicates that RO membranes should be able to effectively remove perchlorate ions. Furthermore, devices certified under *NSF/ANSI Standard 58* have a demonstrated 97 percent perchlorate reduction capability based on reducing perchlorate from challenge level of 130 µg/L to a target level of 4 µg/L.

Boodoo (2003) provides an assessment of possible configurations for POU or point-of-entry ion exchange devices that achieve high removal rates. There are, however, no certification standards for such devices.

5.3 Raw Water Quality Considerations

Because the POU RO devices will be installed at service taps that are downstream of a system's entry point to the distribution system, EPA assumes that the raw water entering a POU RO device will be water that is suitable for consumption except for an exceedance of the proposed perchlorate regulatory standard. As noted in the next section, POU RO devices include pre-filters to address potential interference of delivered water quality with RO performance.

5.4 Pre- and Post-Treatment Needs

POU RO devices include various filters to address pre- and post-treatment concerns. Most devices include a sediment filter for solids removal to prevent membrane fouling and a pre-RO carbon filter to remove chlorine and organic compounds that could impair membrane function. They also include a carbon filter after the membrane and storage tank to remove any organics that may remain or bacterial growth that occurs during storage. Because the POU device is installed at the tap, there are no potential adverse impacts on the distribution system.

5.5 Waste Generation and Residuals Management Needs

The treatment process waste comprises wastewater and used filter cartridges. Waste disposal methods must comply with state and local requirements. The wastewater connection is generally plumbed to the household sewer system, which uses either an on-site septic system or a centralized wastewater collection system for disposal. Depending on state and local regulations, the used cartridge filters may be included in household solid waste (USEPA, 2006b).

5.6 Critical Design Parameters

In addition to the POU devices themselves, there are several components to the design of a POU program that are primary cost drivers. These include the following:

- POU RO device installation
- Public education program development
- POU device monitoring
- POU device maintenance.

Chapter [REF _Ref326047741 \r \h] discusses each of these parameters in more detail and identifies the specific values for each used in EPA's cost estimates.

6 Nontreatment Alternatives

6.1 Application Principle

For small water utilities that lack the financial and/or technical capacity to implement a new treatment-based compliance strategy, nontreatment options may offer a more cost-effective path to compliance. Nontreatment options essentially replace the contaminated water source with water that meets drinking water standards, including a new standard for perchlorate.

Nontreatment solutions for drinking water compliance include the following: well rehabilitation; contaminant source elimination; new well construction; and interconnecting with another system to purchase water (USEPA, 2006c). The feasible nontreatment options will depend on site-specific circumstances such as system size, source water type, contaminant reduction needs, and proximity to alternative water sources. For small systems, neither well rehabilitation for contaminated ground water sources nor source elimination (e.g., remediation of perchlorate-contaminated sediments or ground water) is likely to be feasible and cost-effective solutions. Another option – blending water from existing wells – may be a feasible, low-cost option for systems with multiple wells including some for which perchlorate does not exceed the proposed perchlorate standard. For systems that cannot blend source water to comply with the proposed standard, two feasible nontreatment options include a new well to replace the contaminated source water and an interconnection to purchase water from a supplier. These two options (new wells and interconnection) are likely to have higher costs than the other options (well rehabilitation and source elimination) (USEPA, 2006c).

The costs associated with drilling a new well include the initial hydrological assessment, pilot hole drilling, developing the final well design, drilling the well bore, installing well casings, screens, and filters, development of the well, and installation of the pump and power source (Harter, 2003). A hydrological assessment identifies ground water sources of suitable quality and adequate long-term supply. When replacing an existing well, the costs will also include connecting the well to the existing water distribution system.

The interconnection option involves laying a pipeline to connect the affected system to the distribution network of a neighboring system that can provide adequate water that meets all applicable drinking water standards. Costs include the cost of purchased water as well as construction and maintenance of the interconnection pipeline. Pipeline costs will depend on proximity of the neighboring system, topography of the distance to be covered, and right-of-way requirements for pipes and booster pump stations.

6.2 Compliance Effectiveness

Nontreatment options achieve compliance by replacing a perchlorate-contaminated water source with an alternative water source that meets a perchlorate standard. This strategy is inherently compliant as long as the new water source is not at risk for perchlorate contamination. If the wholesale supplier of purchased water has perchlorate contamination, it must implement an effective treatment process because the water it sells must comply with the perchlorate standard before it can be distributed to the purchasing system.

6.3 Raw Water Quality Considerations

A system will need to determine whether the change in source water may affect other existing treatment processes (e.g., chlorination), or if changes in water quality may affect the distribution system (e.g., purchased water has a different pH). Changes in delivered water chemistry that result in major process additions or changes could diminish the cost-effectiveness of nontreatment options.

6.4 Pre- and Post-Treatment Needs

By definition, there are no pre-treatment needs to consider with a change in source water. All treatment adjustments to account for differences in source water quality would necessarily occur after the point of source water connection. If the alternative water source has chemical parameters that differ substantially from the original source water and may affect water quality elsewhere in the system, then there may be "post-treatment" needs to adjust water chemistry.

6.5 Waste Generation and Residuals Management Needs

An interconnection or new well should not have incremental wastes or residuals requiring management.

6.6 Critical Design Parameters

For new wells, key design parameters are the following:

- Total flow rate requirements and flow per well
- Well depth (and screened depth)
- Pump type
- Distance from well to distribution system.

For an interconnection option, key design parameters include:

- Flow rate requirements
- Distance to interconnection water supply
- Pressure at water supply source
- Cost of purchased water.

Chapter [REF _Ref326047741 \r \h] discusses each of these parameters in more detail and identifies the specific values for each used in EPA's cost estimates.

7 Costs for Treatment Technologies and Nontreatment Options

Note: The technologies evaluated here can achieve very high perchlorate removal efficiencies (e.g., 95 percent or greater). Given the high efficiencies, EPA assumes systems will blend treated water and untreated water to meet the MCL. Accordingly, the costs presented here reflect systems designed and operated to take advantage of the technologies' high removal effectiveness and the cost curves should be applied to design and average flows adjusted to account for the blending rate, as discussed in the following paragraphs.

A blending rate is the proportion of influent water that has to be treated. For example, a blending rate of 0.6 means 60 percent of the water is treated and then blended with 40 percent untreated water. This rate depends on baseline perchlorate concentration, the treatment target concentration, and the removal efficiency of the treatment process (i.e., the percent of baseline perchlorate removed during treatment). For a treatment efficiency of 95 percent (or 0.95), the following equation defines the treatment target concentration of perchlorate (P_t) as a weighted average of the baseline concentration (P_b) and the treated water concentration [P_b x (1-0.95)] where the weights – based on the blending rate, B – are (1-B) for the untreated water and B for the treated water:

$$P_t = (1 - B) \times P_b + B \times (P_b \times (1 - 0.95)).$$

Rearranging terms to solve for B (the blending rate) shows that the blending rate increases when the baseline concentration increases or the treatment target concentration decreases.

$$B = \frac{(P_b - P_t)}{P_b \times 0.95}$$

The cost curves presented here use the treatment process flow as the independent variable. Treatment process flow can be calculated from entry point flow by incorporating the blending rate (B) as follows:

$$Treatment\ Process\ Flow = B \times Entry\ Point\ Flow.$$

7.1 Introduction

7.1.1 Overview and Cost Modeling Approach

This chapter presents estimated costs for installing and operating the technologies and nontreatment options discussed in Chapters [REF _Ref529892942 \r \h] through [REF _Ref529892955 \r \h]. Based on the information in those chapters, particularly the data on engineering design specifications, EPA developed work breakdown structure (WBS) cost estimating models for each of the perchlorate treatment technologies. The WBS models are spreadsheet-based engineering models for individual treatment technologies, linked to a central database of component unit costs. EPA developed the WBS model approach as part of an effort to address recommendations made by the Technology Design Panel (TDP), which convened in 1997 to review the Agency's methods for estimating drinking water compliance costs (USEPA,

1997).[10] In general, the WBS approach involves breaking a process down into discrete components for the purpose of estimating unit costs. The WBS models represent improvements over past EPA cost estimating methods by increasing comprehensiveness, flexibility, and transparency. By adopting a WBS-based approach to identify the components that should be included in a cost analysis, the models produce a more comprehensive assessment of the capital and operating requirements for a treatment system. The documentation for the individual WBS models (USEPA, 2018, 2017a-c, 2007) provides complete details on the structure, content, and use of the models. EPA used the WBS models to develop the costs presented in this chapter.

The remainder of this section provides a brief overview of the common elements of all the WBS models and information on the anticipated accuracy of the resulting cost estimates. Subsequent sections describe how EPA used each individual technology-specific WBS model to estimate costs for perchlorate treatment and present the resulting cost estimates.

7.1.2 Work Breakdown Structure Models

Each WBS model contains the work breakdown for a particular treatment process and preprogrammed engineering criteria and equations that estimate equipment requirements for user-specified design requirements (e.g., system size and influent water quality). Each model also provides unit and total cost information by component (e.g., individual items of capital equipment) and totals the individual component costs to obtain a direct capital cost. Additionally, the models estimate add-on costs (permits, pilot study, and land acquisition costs for each technology), indirect capital costs, and annual operation and maintenance (O&M) costs, thereby producing a complete compliance cost estimate.

Primary inputs common to all of the WBS models include design flow and average flow in MGD. Each WBS model has default designs (input sets) that correspond to the eight standard flow sizes in EPA's flow characterization paradigm for public water systems (see **[REF _Ref256672992 \h * MERGEFORMAT]**), but the models can generate designs for many other combination of flows. To estimate costs for perchlorate compliance, EPA fit cost curves to the WBS estimates for up to 49 different flow rates.[11] Thus, the cost estimates in Sections [REF _Ref326230172 \r \h] through [REF _Ref329773612 \r \h] and Appendix B are in the form of equations.

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[10] The TDP consisted of nationally recognized drinking water experts from U.S. EPA, water treatment consulting companies, public and private water utilities and suppliers, equipment vendors, and Federal and State regulators in addition to cost estimating professionals.

[11] Specifically, for each scenario modeled and separately for total capital and for O&M costs, EPA fit up to three curves: one covering small systems (less than 1 MGD design flow), one covering medium systems (1 MGD to less than 10 MGD design flow), and one covering large systems (10 MGD design flow and greater). For each curve fit, EPA chose from among several possible equation forms: linear, quadratic, cubic, power, exponential, and logarithmic. EPA chose the form that resulted in the best correlation coefficient (R^2), subject to the requirement that the equation must be monotonically increasing over the appropriate range of flow rates (i.e., within the flow rate category, the equation must always result in higher estimated costs for higher flow systems than for lower flow systems).

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Model Size Categories Based on EPA's Flow Characterization Paradigm

Size Category	Population Served	Design Flow (MGD)	Average Flow (MGD)
1	25 to 100	0.030	0.007
2	101 to 500	0.124	0.035
3	501 to 1,000	0.305	0.094
4	1,001 to 3,300	0.740	0.251
5	3,301 to 10,000	2.152	0.819
6	10,001 to 50,000	7.365	3.200
7	50,001 to 100,000	22.614	11.087
8	Greater than 100,000	75.072	37.536

Another input common to all of the WBS models is "component level" or "cost level." This input drives the selection of materials for items of equipment that can be constructed of different materials. For example, a low cost system might include fiberglass pressure vessels and PVC piping. A high cost system might include stainless steel pressure vessels and stainless steel piping. The component level input also drives other model assumptions that can affect the total cost of the system, such as building quality and heating and cooling. The component level input has three possible values: low cost, mid cost, and high cost. To estimate costs for perchlorate compliance, EPA generated separate cost curves for each of the three component levels, thus creating a range of cost estimates for use in national compliance cost estimates.

The third input common at all of the WBS models is system automation, which allows the design of treatment systems that are operated manually or with varying degrees of automation (i.e., with control systems that reduce the need for operator intervention). The cost estimates in the technology-specific sections below are for systems that are fully automated, minimizing the need for operator intervention and reducing operator labor costs.

The WBS models generate cost estimates that include a consistent set of capital, add-on, indirect, and O&M costs. **[REF _Ref256677692 \h * MERGEFORMAT]** identifies these cost elements, which are common to all of the WBS models and included in the cost estimates below. The exhibit also provides references for further information on the methods and assumptions used in the WBS models to estimate the costs for each of these cost elements.

7.1.3 WBS Model Accuracy

Costs for a given system can vary depending on site-specific conditions (e.g., raw water quality, climate, local labor rates, and location relative to equipment suppliers). The costs presented here are based on national average assumptions and include a range (represented by low, mid, and high cost curves) intended to encompass the variation in costs that systems would incur to remove perchlorate. To validate the engineering design methods used by the WBS models and increase the accuracy of the resulting cost estimates, EPA has subjected the individual models to a process of external peer review by nationally recognized technology experts.

The anion exchange model underwent peer review in 2005, during an early stage of its development. One peer reviewer responded that resulting cost estimates were in the range of budget estimates (+30 to -15 percent). The other two reviewers thought anion exchange estimates were order of magnitude estimates (+50 to -30 percent), with an emphasis on the estimates being

high. The anion exchange model has since undergone extensive revision, both in response to the peer review and to adapt it for perchlorate treatment (see Section [REF _Ref326230172 \r \h], below).

The RO/NF model underwent peer review in 2007. The majority of peer reviewers who evaluated the model expressed the opinion that resulting cost estimates would be in the range of budget estimates (+30 to -15 percent). The RO/NF model has since undergone substantial revision in response to the peer review comments.

The biological treatment model underwent peer review in early 2012. One reviewer thought the model underestimated O&M costs by 20 to 30 percent (which would be in the range of an order of magnitude estimate), but overestimated capital costs by about 25 percent (which would be in the range of a budget estimate). A second reviewer responded that direct capital costs were at the fringes of a budget estimate (+30 to -15 percent), while total capital costs were in the order of magnitude range (+50 to -30 percent) or possibly even better, in the budget estimate range. This reviewer's conclusions about total capital costs were based on comparison to preliminary costs for a plant currently under construction, for which the model underestimated costs. The final reviewer responded that costs were budget estimates (+30 to -15 percent). The biological treatment model has since undergone revision in response to the peer review comments.

The POU model underwent peer review in 2006. Reviewers felt that the default assumptions may tend to overstate "out-of-pocket" costs to systems because very small systems could use volunteers to perform some tasks. While this may be true, EPA's model is designed to estimate the opportunity costs for a successful POU program that is consistent with EPA POU Guidance, which does not include volunteers. The POU model has since been revised in response to the peer review comments.

EPA received peer review comments on the nontreatment model in May 2012. The first reviewer responded that cost estimates resulting from the nontreatment model were in the range of budget estimates (+30 to -15 percent). The second reviewer thought the cost estimates were order of magnitude estimates (+50 to -30 percent). The third reviewer felt the cost estimates were definitive (+15 to -5 percent), except for land costs, which were difficult to assess due to regional variations. Revision of the nontreatment model in response to the peer review comments was recently completed.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Cost Elements Included in All WBS Models

Cost Category and Components Included	For Further Information
Direct Capital Costs	
• Technology-specific equipment (e.g., vessels, basins, pumps, blowers, treatment media, piping, valves)	Technology-specific sections below
• Instrumentation and system controls	USEPA (2018, 2017a-c), Appendix A
• Buildings	USEPA (2018, 2017a-c), Appendix B
• Residuals management equipment	USEPA (2018, 2017a-c), Appendix C
Add-on Costs	
• Land • Permits • Pilot testing	USEPA (2018, 2017a-c), Chapter 2
Indirect Capital Costs	
• Mobilization and demobilization • Architectural fees for treatment building • Equipment delivery, equipment installation, and contractor's overhead and profit • Sitework • Yard piping • Geotechnical • Standby power • Electrical infrastructure • Process engineering • Contingency • Miscellaneous allowance • Legal, fiscal, and administrative • Sales tax • Financing during construction • Construction management	USEPA (2018, 2017a-c), Appendix D
O&M Costs	
• Operator labor for technology-specific tasks (e.g., managing regeneration, backwash, or media replacement) • Materials for maintenance and operation of technology-specific equipment • Replacement of technology-specific equipment that occurs on an annual basis (e.g., treatment media) • Energy for operation of technology-specific items of equipment (e.g., blowers, mixers)	Technology-specific sections below
• Operator labor for operation and maintenance of process equipment • Operator labor for building maintenance • Managerial and clerical labor • Materials for maintenance of booster or influent pumps • Materials for building maintenance • Energy for operation of booster or influent pumps • Energy for lighting, ventilation, cooling, and heating	USEPA (2018, 2017a-c), Appendix E
• Residuals management operator labor, materials, and energy • Residuals disposal and discharge costs	USEPA (2018, 2017a-c), Appendix C

7.2 Costs for Ion Exchange

7.2.1 Model Components and Assumptions

USEPA (2017a) provides a complete description of the engineering design process used by the WBS model for perchlorate ion exchange. The perchlorate ion exchange model can estimate costs for removing perchlorate using any of the following resin types described Chapter 2: strong-base polyacrylic, strong-base polystyrenic, nitrate-selective, and perchlorate-selective.[12] In addition to the common WBS direct capital cost items listed in **[REF _Ref256681355 \h * MERGEFORMAT]**, the ion exchange model for perchlorate includes the following technology-specific equipment:

- Booster pumps for influent water
- Pressure vessels that contain the anion resin bed
- Tanks and pumps for backwashing the vessels
- Tanks, mixers, and eductors for delivering the solution used in regenerating the resin (if regeneration is used)
- Pre-treatment cartridge filters
- Tanks and pumps for post-treatment corrosion control (optional)
- Equipment for managing residuals (spent backwash, spent resin, and, potentially, spent regenerant)
- Associated piping, valves, and instrumentation.

The ion exchange model for perchlorate also adds the following technology-specific O&M elements:

- Operator labor for resin changeouts
- Operator labor for regeneration (if regeneration is used)
- Spent resin replacement and disposal
- Labor and replacement cartridges for pre-treatment filters
- Chemical usage (if corrosion control or regeneration is used).

For small systems (less than 1 MGD), the ion exchange model for perchlorate assumes the use of package treatment systems that are pre-assembled in a factory, mounted on a skid, and transported to the site. The model estimates costs for package systems by costing all individual equipment line items (e.g., vessels, interconnecting piping and valves, instrumentation, and system controls) in the same manner as custom-engineered systems. This approach is based on vendor practices of partially engineering these types of package plants for specific systems (e.g., selecting vessel size to meet flow and treatment criteria). The model applies a variant set of design inputs and assumptions that are intended to simulate the use of a package plant and that reduce the size and cost of the treatment system. USEPA (2017a) provides complete details on the variant design assumptions used for package plants.

[12] The input also allows for selection of an alternative resin type, by entering appropriate design assumptions for their resin and selecting "Alternative resin (user defined)" for this input.

The paragraphs below describe the specific inputs and assumptions that EPA used to generate the costs in Section [REF _Ref329333708 \r \h]. These inputs assume treatment with perchlorate breakthrough defined so that the treatment process maintains a minimum of 95 percent removal. Other inputs and assumptions not discussed below (e.g., number of booster pumps, treated water corrosion control, bed expansion) remained as described in USEPA (2017a).

Resin Type

As noted above, the perchlorate ion exchange model can estimate costs for removing perchlorate using several different resin types. Based on the information in Section [REF _Ref286409819 \r \h] and **[REF _Ref286411968 \h * MERGEFORMAT]**, however, EPA believes that any new ion exchange facilities removing perchlorate will use perchlorate-selective resin. Therefore, the cost estimates below assume the use of perchlorate-selective resin and, accordingly, the paragraphs below describe the inputs and assumptions associated with perchlorate-selective resins only.

Regeneration or Throwaway Operation

The perchlorate ion exchange model has an option to design and estimate costs for a system either with or without regeneration capability. As discussed in Section [REF _Ref292805680 \r \h], nearly all of the full-scale facilities using perchlorate-selective resin rely on disposal instead of regeneration. Therefore, the cost estimates below assume throwaway operation.

Number of Bed Volumes before Regeneration/Throwaway

The perchlorate ion exchange model requires entry of the number of bed volumes before perchlorate breakthrough. System configuration (i.e., parallel or series operation) can have a significant effect on bed volumes to breakthrough. As discussed below, the model default assumption is series (lead-lag) operation. The data shown in **[REF _Ref286412546 \h * MERGEFORMAT]** are for initial perchlorate breakthrough using a single resin column. Studies of the capacity of the older perchlorate-selective resin (Gu et al., 1999) found breakthrough in a lead column after 40,000 BV. Using a second (lag or polishing) column increased the resin's capacity to approximately 104,000 BV. Similar studies of the performance of the new resins in a lead-lag configuration are not available.

Given the lack of precise data on the performance of the new resins in a lead-lag configuration and given expected site-specific variations in water quality (e.g., concentrations of competing anions), the cost estimates below consider two scenarios for bed life. Although one of the scenarios assumes a longer bed life than the other (meaning better performance and lower costs), both scenarios are designed to be conservative (erring on the site of higher costs).

The first scenario assumes an increase in capacity of the new resins from lead-lag operation similar to that observed for the older resin. This scenario starts from the lowest single-column capacity (about 100,000 BV) observed for any of the new resins in several pilot studies (Blute et al., 2006; Russell et al., 2008; Wu and Blute, 2010). It multiplies this capacity by 2.5 (the approximate increase observed for the older resin in Gu et al., 1999) to account for lead-lag operation. This calculation results in 250,000 BV to breakthrough. The second scenario starts from the highest single-column capacity (about 170,000 BV) observed for any of the new resins

the pilot studies, but assumes no increase in capacity from lead-lag operation. Thus, the second scenario assumes 170,000 BV to breakthrough.

Number of Vessels in Series (parallel or series operation)

As discussed in Section [REF _Ref292959102 \n \h], series (lead-lag) operation is generally recommended for perchlorate removal. Therefore, the cost estimates below assume two vessels in series.

Theoretical Total Empty Bed Contact Time

As discussed in Section [REF _Ref292959102 \n \h], recommended EBCTs for perchlorate-selective resins are 1.5 minutes per vessel and less. Therefore, the cost estimates below assume a total EBCT of 3 minutes (which corresponds to 1.5 minutes per vessel, given two vessels in series).

Backwash System Design

The perchlorate ion exchange model assumes that periodic backwashing during operation is not required when throwaway operation is chosen. It does, however, assume an initial rinse is required during resin installation. Therefore, for systems of 1 MGD design flow and larger the cost estimates below include the cost of equipment (pumps and storage tanks) to accomplish this initial rinse. For small systems, the cost estimates assume the initial rinse can be accomplished using existing equipment.

Residuals Management

The perchlorate ion exchange model includes the option to dispose of spent resin by incineration.[13] As discussed in Section [REF _Ref292960035 \n \h], a number of full-scale facilities dispose of their spent perchlorate-selective resin by incineration. Although incineration is a more expensive option than landfill disposal, the overall impact on operating costs is small. Incineration increases model cost estimates by approximately $0.01 per thousand gallons of treated water produced, which is less than 3 percent of the total cost of treatment even for the largest systems. Therefore, the cost estimates below assume disposal by incineration, although some systems might have the slightly cheaper option of landfill disposal available. They assume that spent rinse water from the initial resin rinse is discharged to a POTW.

Surface Loading Rate

As discussed in Section [REF _Ref292959102 \n \h], maximum surface loading rates vary by resin type. Based on the data presented in Section [REF _Ref292959102 \n \h] and comments from the experts who reviewed initial drafts of this document (Meyer, 2012; Blute, 2012; Drago,

[13] This option is activated by entering the cost of incineration under "Alternate media disposal cost (including transportation)" in the O&M assumptions module of the perchlorate version of the ion exchange model. When a value is present for this assumption, the model uses this unit cost in estimating total non-hazardous waste disposal cost. If this assumption is left blank, the model uses the default unit cost from the central WBS database, which reflects disposal in an off-site non-hazardous waste landfill.

2012), EPA chose a maximum surface loading rate of 12 gpm/ft^2 for perchlorate-selective resin. The cost estimates below incorporate this assumption.

Regeneration Solution Type and Assumptions

The perchlorate ion exchange model incorporates the option to regenerate selective resins using the novel tetrachloroferrate regeneration solution discussed in Section [REF _Ref292709289 \n \h]. Specifically, when regeneration is chosen for nitrate- or perchlorate-selective resins, the model assumes the use of tetrachloroferrate solution. When regeneration is chosen for non-selective strong-base polyacrylic or polystyrenic resins, the model assumes the use of conventional brine solution. The selection of resin type also controls the values of a number of critical design assumptions relevant to each regeneration process (e.g., brine concentration, tetrachloroferrate solution strength, regeneration time). The cost estimates below, however, assume throwaway operation and, therefore, do not incorporate these assumptions.

7.2.2 Cost Estimates

The graphs below plot WBS cost model results in 2017 dollars at the mid cost level for removal of perchlorate from groundwater using perchlorate-selective ion exchange, assuming 250,000 BV to breakthrough (**[REF _Ref292961817 \h * MERGEFORMAT]**) and 170,000 BV to breakthrough (**[REF _Ref292961823 \h * MERGEFORMAT]**). The costs assume treatment with perchlorate breakthrough defined so that the treatment process maintains a minimum of 95 percent removal. The flow rates shown on the x-axes and as independent variables in the equations are treatment process flows. To account for blending, treatment process flows should be calculated from entry point flows by incorporating a blending rate as discussed in the introduction to this chapter.

In these exhibits, note that costs increase at 1 MGD design flow (0.355 MGD average flow) because of the transition from package systems (used by small systems) to custom-engineered systems (used by large systems). Appendix B provides complete cost equations for both bed life scenarios, including the high, mid, and low cost levels and for treatment of groundwater and surface water. Appendix C presents example WBS model outputs at selected flow rates, allowing review of individual cost line items.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Mid Cost Results for Removal of Perchlorate from Groundwater Using Perchlorate-Selective Ion Exchange with 250,000 BV to Breakthrough (2017 dollars)

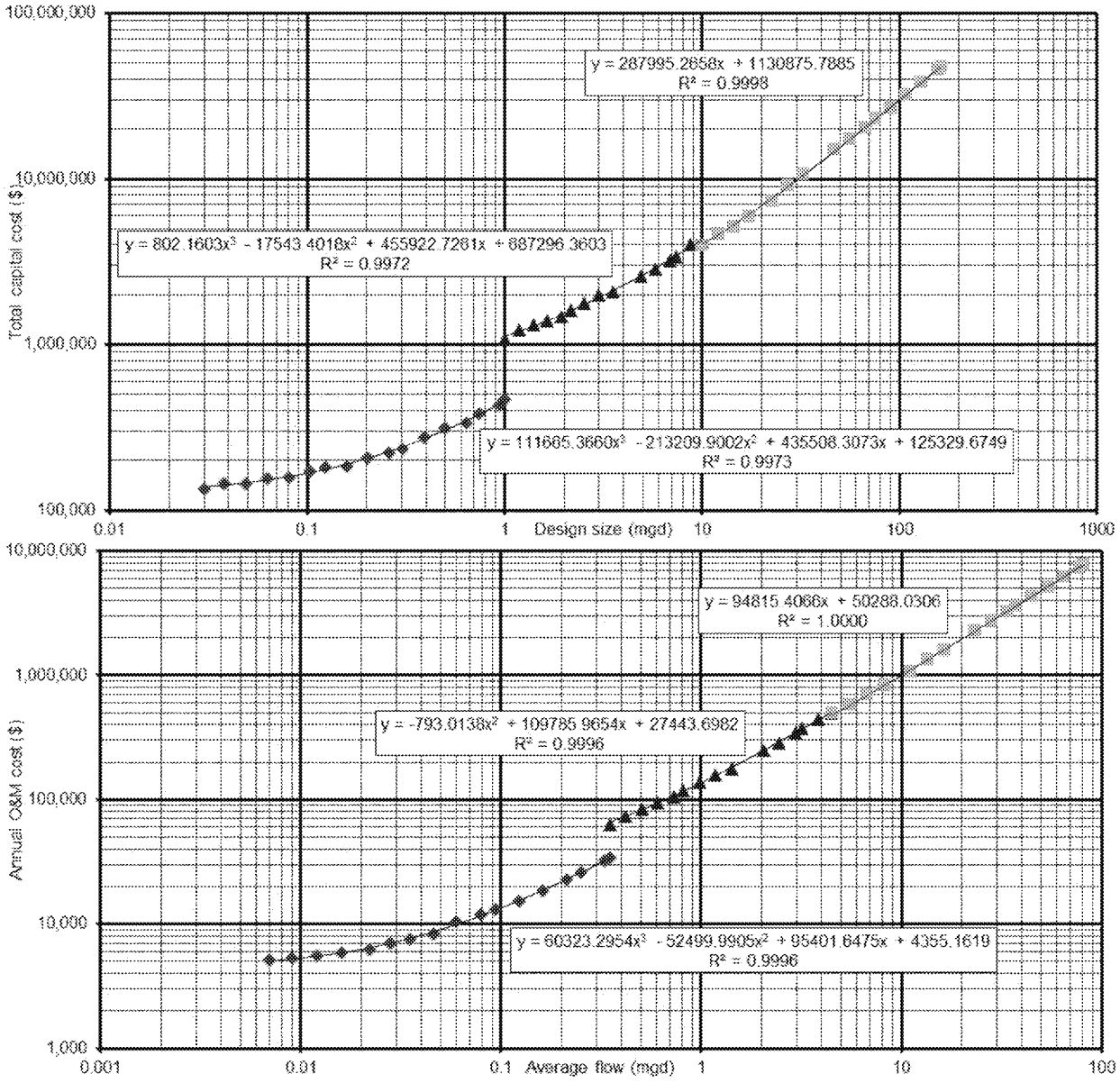
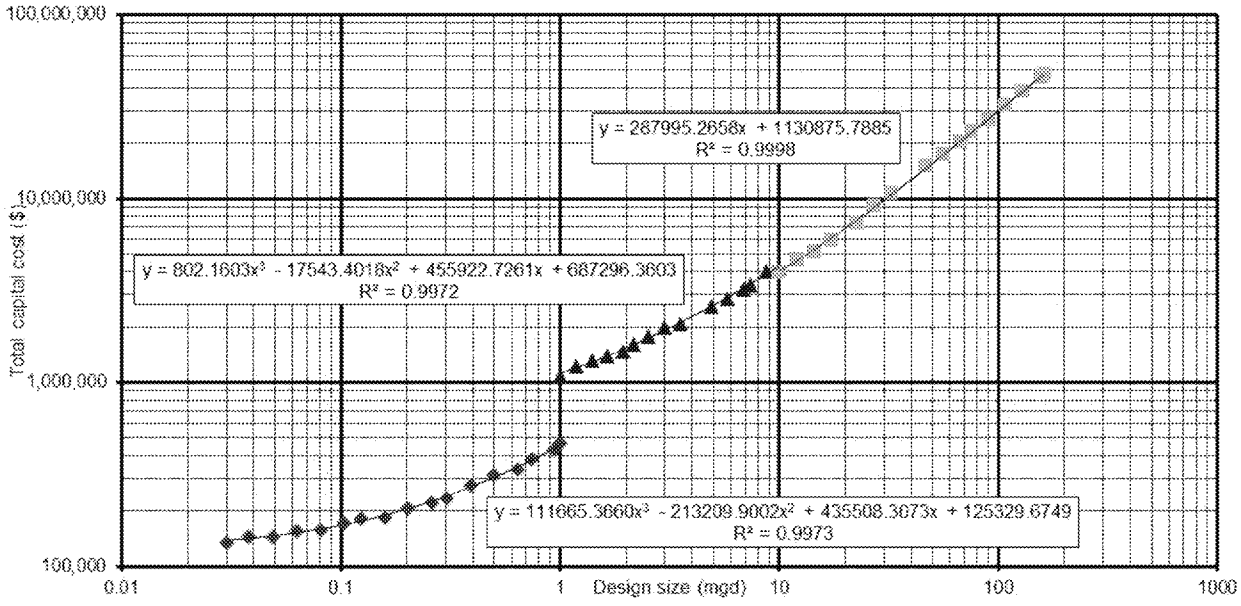
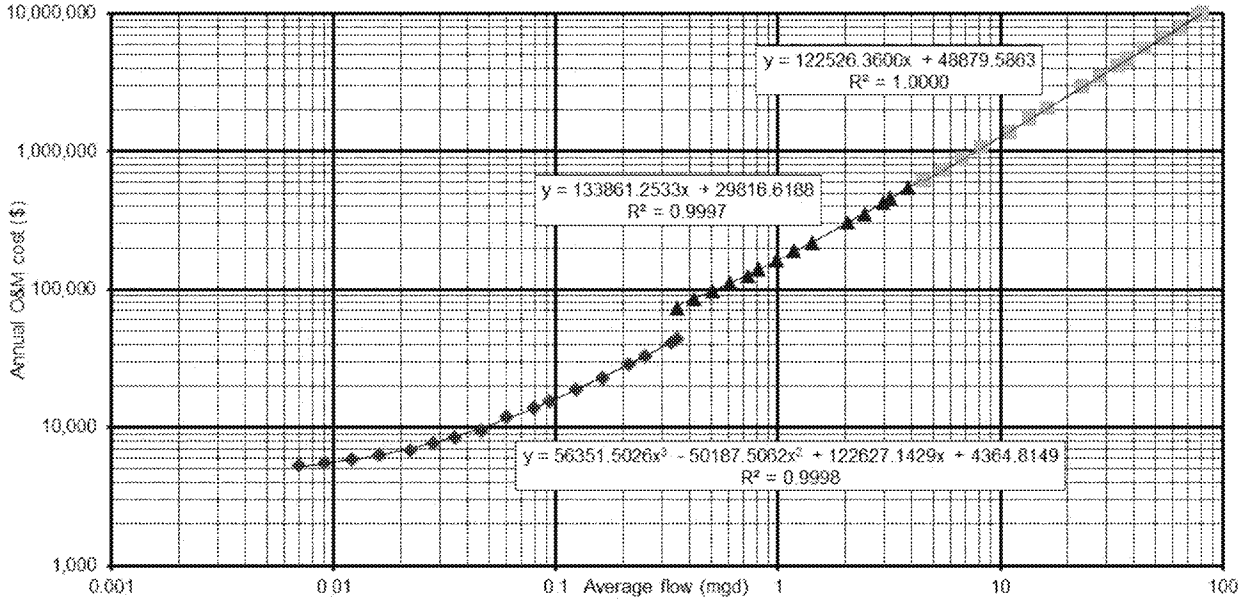


Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Mid Cost Results for Removal of Perchlorate from Groundwater Using Perchlorate-Selective Ion Exchange with 170,000 BV to Breakthrough (2017 dollars)





7.3 Costs for Biological Treatment

7.3.1 Model Components and Assumptions

USEPA (2017b) provides a complete description of the engineering design process used by the WBS model for biological treatment. The biological treatment model can estimate costs for three types of bioreactor designs:

- Fixed media bed pressure vessels
- Fixed media bed gravity basin
- Fluidized bed pressure vessels.

In addition to the common WBS direct capital cost items listed in **[REF _Ref256677692 \h * MERGEFORMAT]**, the biological treatment model includes the following technology-specific equipment:

- Booster pumps for influent water
- Equipment (e.g., tanks, pumps) for electron donor addition
- Equipment (e.g., tanks, pumps) for nutrient addition
- Bioreactors (either pressure vessels or concrete basins) that contain the GAC media bed
- Tanks, pumps, and blowers for backwashing the bioreactors (fixed bed designs only) and post-treatment filters (if used)
- Pumps for recycled water (fluidized designs only)
- Blowers for biomass separation (fluidized designs only)
- Equipment for post-treatment aeration or hydrogen peroxide addition (optional)
- Post-treatment coagulant addition and mixed media filtration (optional)
- Equipment for managing residuals (spent backwash)
- Associated piping, valves, and instrumentation (including online perchlorate and nitrate analysis instruments).

The biological treatment model also adds the following technology-specific O&M elements:

- Operator labor for managing backwashes
- Operator labor and materials for maintaining concrete basins (gravity designs only)
- Operator labor and materials for maintaining backwash pumps and air scour blowers (and biomass removal blowers for fluidized bed designs)
- Chemical usage for electron donor and nutrient addition (and post-treatment hydrogen peroxide addition, if used)
- Coagulant and polymer usage for spent backwash treatment (and post-treatment filtration, if used)
- Attrition loss replacement for bioreactor media (and post-treatment filter media, if used)
- Consumables used in online perchlorate and nitrate analysis.

For small systems (less than 1 MGD), the biological treatment model applies a set of design inputs and assumptions that reduce the size and cost of the treatment system relative to larger systems. Some of these small system assumptions are similar to those used for package plants in the ion exchange model (e.g., skid-mounted pressure vessels, reduced need for booster pumping). Because package plants are not currently available for biological treatment, however,

the biological treatment model assumptions do not differ as greatly between small and large systems. USEPA (2017b) provides complete details on the variant design assumptions used for small systems.

The paragraphs below describe specific inputs and assumptions that EPA used to generate the costs in Section [REF _Ref326051577 \r \h * MERGEFORMAT]. Other inputs and assumptions not discussed below (e.g., number of booster pumps, bioreactor dimensions) were as described in USEPA (2017b).

Electron Donor Type

The biological treatment model allows the user to select between acetic acid and ethanol as the electron donor type. As discussed in Section [REF _Ref326052320 \r \h * MERGEFORMAT], these are the most common electron donors used in full-scale biological systems treating perchlorate. The cost estimates below assume acetic acid as the electron donor.

Electron Donor Dose

As discussed in Section [REF _Ref326052320 \r \h * MERGEFORMAT], electron donor dose is typically determined using pilot studies along with stoichiometric calculations. The biological treatment model requires the user to input the electron donor dose. For comparison purposes, the user can enter raw waster quantities of perchlorate, nitrate, and dissolved oxygen and the model will display the results of stoichiometric calculations using the site-specific equations discussed in Section [REF _Ref326052320 \r \h * MERGEFORMAT]. The cost estimates below assume 10 mg/L of acetic acid.

Nutrient Requirements

The biological treatment model includes four options for nutrient addition:

- no additional nutrients required
- additional nitrogen required
- additional phosphorous required
- both nitrogen and phosphorous required.

For designs that require additional nutrients, the model prompts the user to input doses for ammonium chloride and/or phosphoric acid. Based on comments from the peer review of the biological treatment model, the cost estimates below assume additional phosphorous is required and achieved using 1 mg/L (measured as phosphorus) of phosphoric acid.

Empty Bed Contact Time/Hydraulic Residence Time

The biological treatment model uses EBCT in sizing fixed bed bioreactors and HRT in sizing fluidized bed bioreactors. As discussed in Section [REF _Ref326052320 \r \h * MERGEFORMAT], typical full-scale bioreactor designs have an EBCT/HRT in the range of 10 to 12 minutes for both fixed bed (U.S. DoD, 2008b) and fluidized bed reactors (Harding ESE, 2001). The cost estimates below assume an EBCT/HRT value of 12 minutes.

Interval between Backwashes

For fixed bed bioreactors, the biological treatment model requires the user to input the interval between backwashes.[14] For designs that include post-treatment filters (see below), the model requires a separate backwash interval for these filters. The cost estimates below assume backwash intervals of 24 hours for fixed bed bioreactors and 36 hours for post-treatment filters.

Post-Treatment Options

Biological treatment results in the production of soluble microbial organic products that become part of the treated water. The biological treatment process also depletes the levels of oxygen in the treated water. Therefore, based on peer review comments, post-treatment will be required for production of drinking water. The biological treatment model allows users to choose whether to include post-treatment coagulant addition and filtration for removal of turbidity, sulfide, and/or dissolved organic content. It also allows users to choose from aeration or hydrogen peroxide addition for post-treatment oxidation. The cost estimates below include post-treatment filtration with coagulant addition and aeration for post-treatment oxidation.

Although post-treatment disinfection typically is needed following biological treatment, disinfection is required for most water systems regardless of whether perchlorate treatment is present. Therefore, the costs of disinfection are not attributable exclusively to perchlorate compliance. Accordingly, the cost estimates below do not include post-treatment disinfection; they assume that existing disinfection facilities are sufficient and located appropriately.

Fluidized Bed Expansion

Based on peer review comments on the biological treatment model, the cost estimates below assume bed expansion of 70 percent for fluidized beds. They also include freeboard above the expanded bed of 4 feet for small systems (less than 1 MGD design flow) and 7 feet for larger systems (1 MGD and greater).

Fluidized Bed Recycle Rate

Based on peer review comments on the biological treatment model, the cost estimates below assume a recycle rate of 50 percent for fluidized beds.

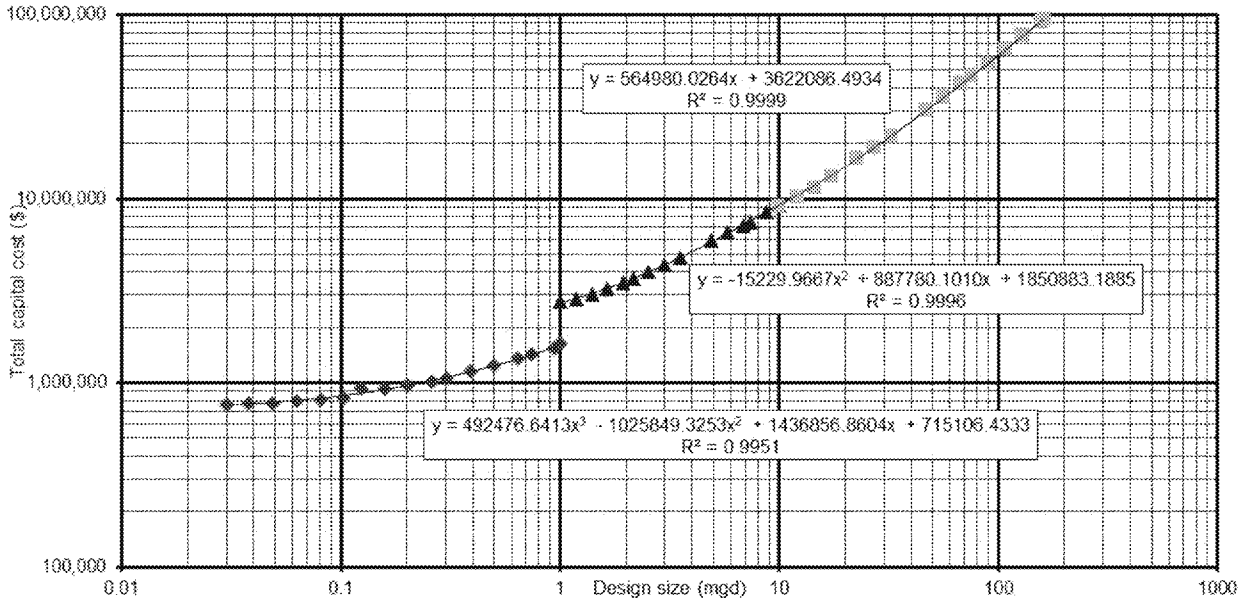
7.3.2 Cost Estimates

The graphs below plot WBS cost model results in 2017 dollars at the mid cost level for removal of perchlorate from groundwater using biological treatment with fixed bed pressure vessels (**[REF _Ref326062889 \h * MERGEFORMAT]**), fixed bed gravity basins (**[REF _Ref326062900 \h * MERGEFORMAT]**), and fluidized bed pressure vessels (**[REF _Ref329596213 \h * MERGEFORMAT]**). In the exhibits, note that costs increase at 1 MGD design flow (0.355 MGD average flow) because of the change in assumptions used for small systems versus those for large systems. Appendix B provides complete cost equations for all three design types, including the high, mid, and low cost levels and for treatment of groundwater

[14] For fluidized bed bioreactors, the model uses a continuous biomass separation device consisting of a blower to agitate excess biomass and send it out of the bioreactor in the effluent, so no such interval is needed.

and surface water. Appendix C presents example WBS model outputs for selected flow rates, allowing review of individual cost line items.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Mid Cost Results for Removal of Perchlorate from Groundwater Using Biological Treatment with Fixed Bed Pressure Vessels (2017 dollars)



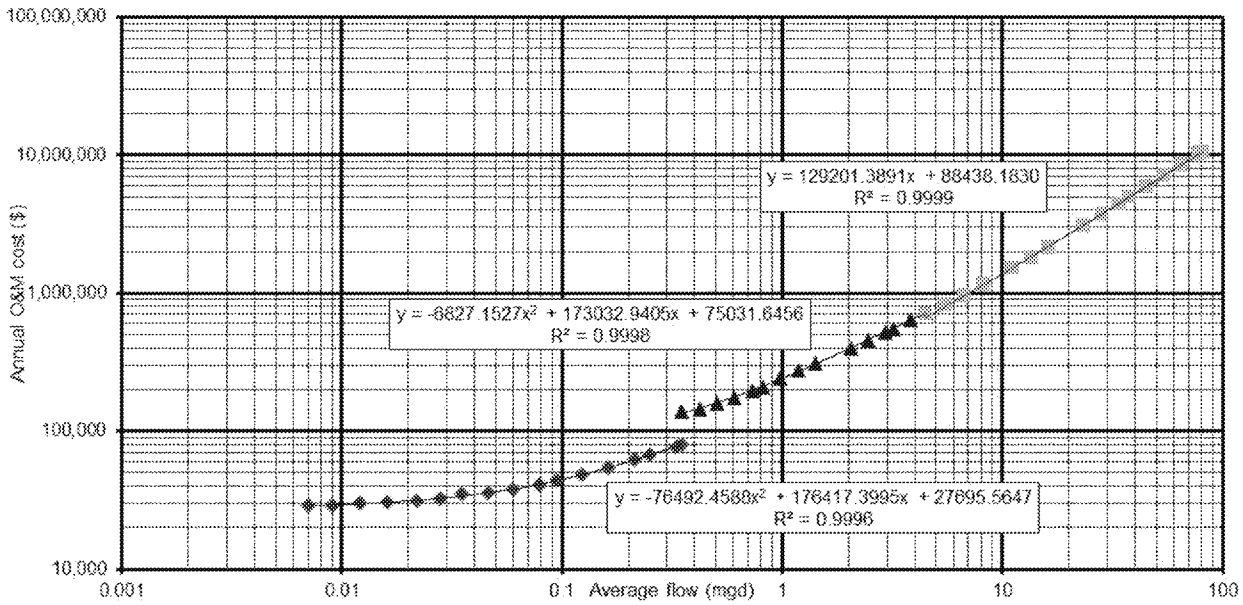
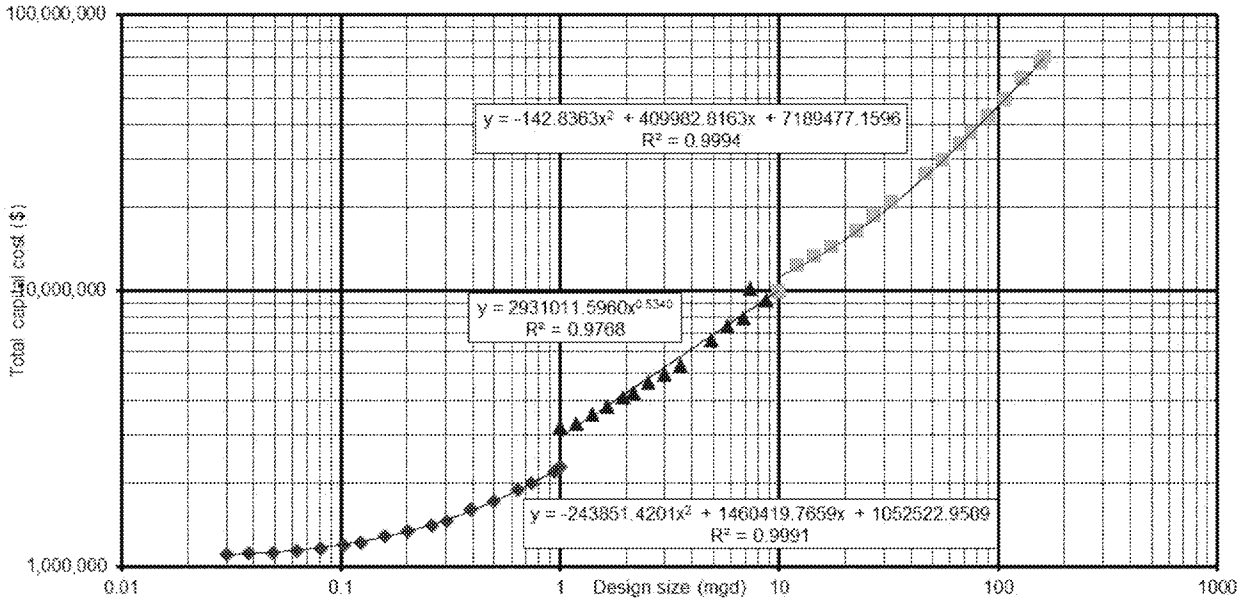


Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Mid Cost Results for Removal of Perchlorate from Groundwater Using Biological Treatment with Fixed Bed Gravity Basins (2017 dollars)



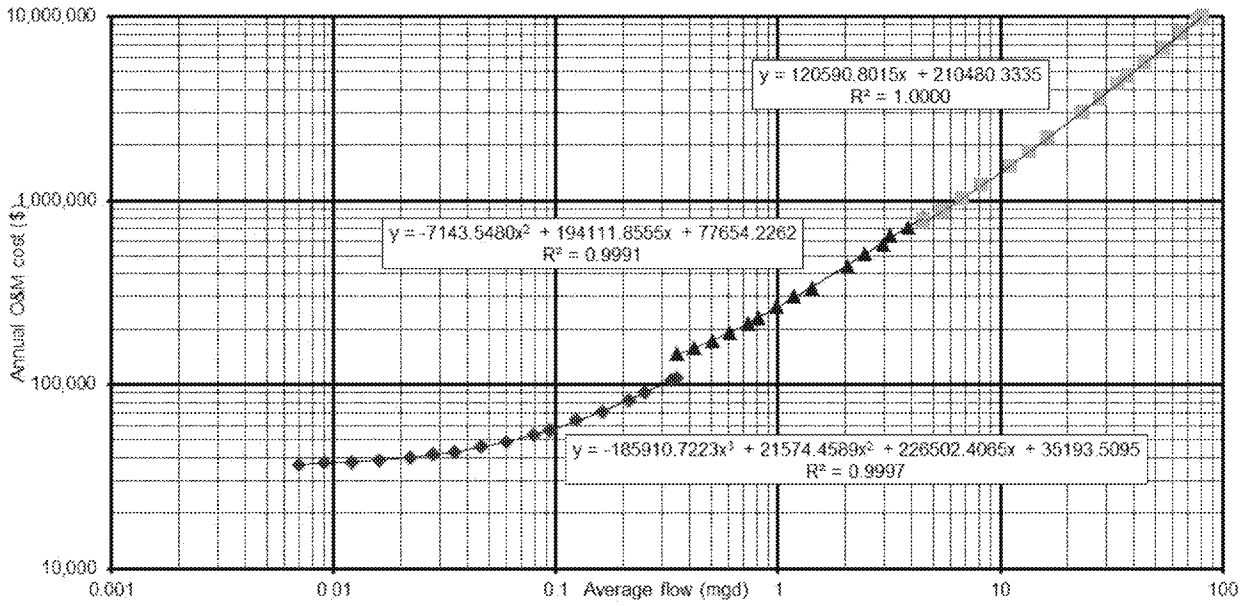
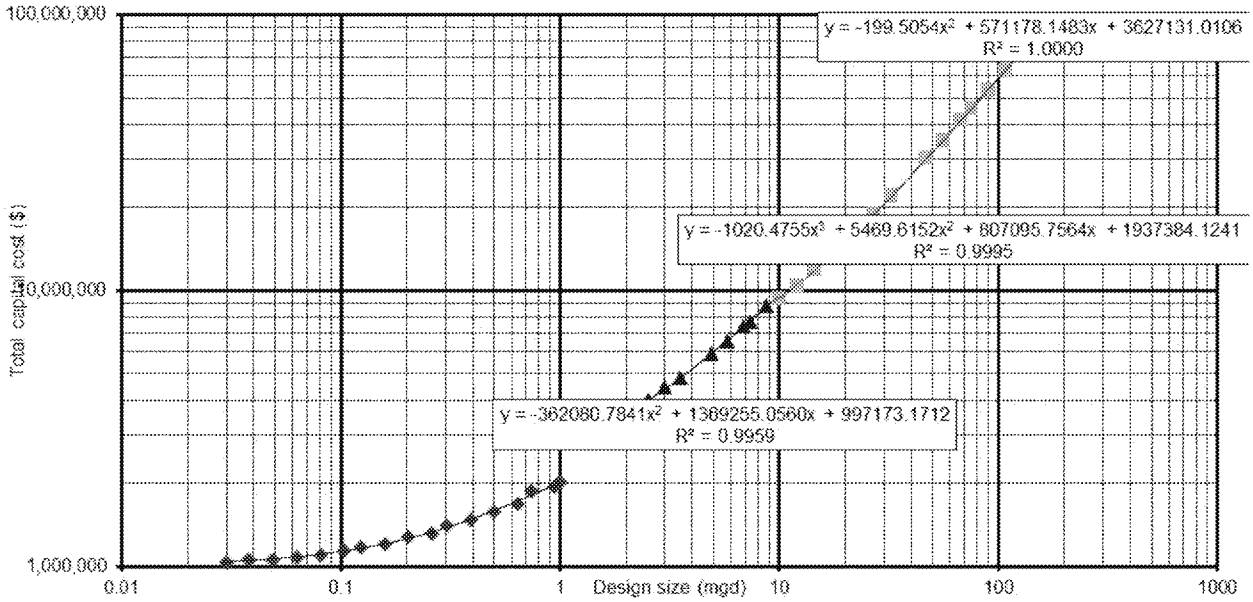
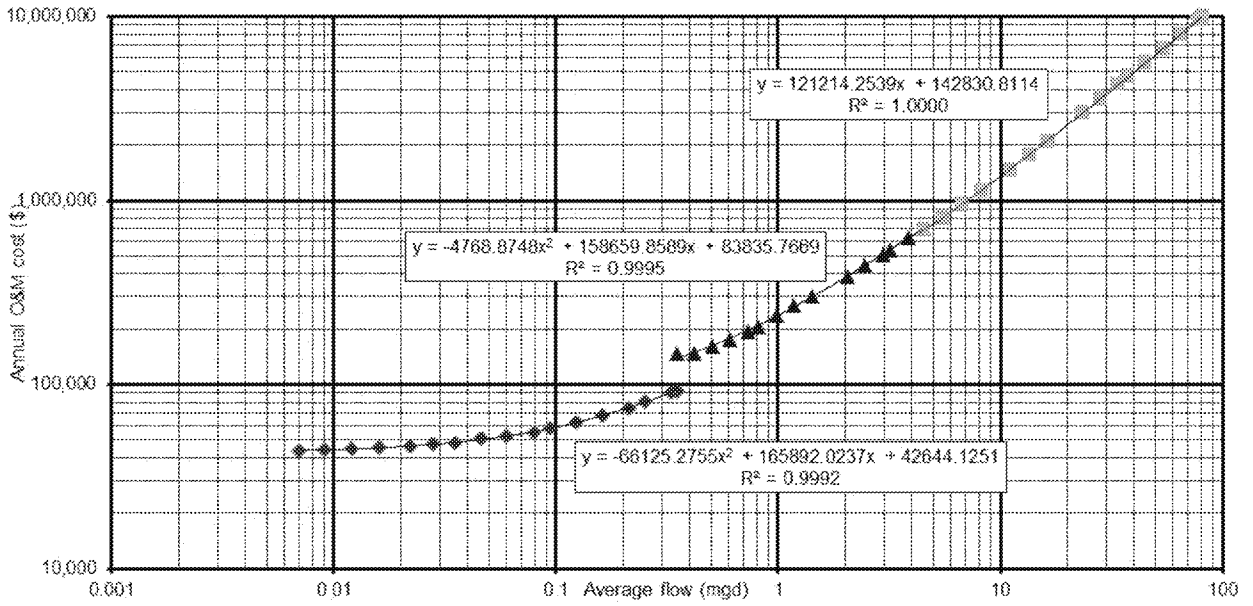


Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Mid Cost Results for Removal of Perchlorate from Groundwater Using Biological Treatment with Fluidized Bed Pressure Vessels (2017 dollars)





7.4 Costs for Reverse Osmosis

7.4.1 Model Components and Assumptions

USEPA (2018) provides a complete description of the engineering design process used by the WBS model for RO/NF. The model can estimate costs for a multistage RO installation, based on an input water quality analysis and treatment parameters. Although it is also capable of estimating costs for NF, the model was used here specifically for RO, because that membrane technology showed the most promise for removing perchlorate. As discussed in Chapter [REF _Ref329770602 \r \h], NF (and UF) demonstrated widely varying removal of perchlorate.

In addition to the common WBS direct capital cost items listed in **[REF _Ref256677692 \h * MERGEFORMAT]**, the RO model includes the following technology-specific equipment:

- Pressure vessels, membrane elements, piping, valves, connectors, and steel structure for the membrane racks
- High-pressure pumps for influent water and (optionally) interstage pressure boost
- Valves for concentrate control and (optionally) per-stage throttle
- Cartridge filters for pretreatment
- Tanks, pumps, and mixers for pretreatment chemicals
- Tanks, pumps, screens, cartridge filters, and heaters for membrane cleaning
- Equipment for managing RO concentrate and spent cleaning chemicals
- Associated pipes, valves, and instrumentation.

The RO model also includes the following technology-specific O&M elements:

- Operator labor and replacement elements for pretreatment cartridge filters
- Chemical usage for pretreatment
- Labor and materials for routine operation and maintenance of membrane units
- Energy for high-pressure pumping
- Replacement of membrane elements
- Labor, materials, and chemical usage for membrane cleaning
- Disposal costs for spent cartridge filters and membrane elements
- Fee for disposal of concentrate at a POTW (if POTW disposal is selected).

The paragraphs below describe specific inputs and assumptions that EPA used to generate the costs in Section [REF _Ref329770828 \r \h * MERGEFORMAT]. Other inputs and assumptions not discussed below (e.g., cleaning interval, permeate throttling and interstage boost, membrane life) were as described in USEPA (2018).

Water Type

As described in Section [REF _Ref329784338 \r \h], the composition of the feed water affects pretreatment and cleaning requirements, the range of permissible RO train design parameters, and energy usage for pumping. The WBS model includes three default ground waters and three default surface waters, ranging from high to low quality (i.e., from low to high total dissolved solids and scaling potential). The particular water parameters are based on a survey of membrane feed water characteristics in the literature. The cost estimates below and in Appendix B are intended to reflect the incremental cost of removing perchlorate from otherwise deliverable water

using RO. Therefore, they use the default high quality water parameters built in to the WBS model. Total dissolved solids for the high quality surface water is approximately 360; for high quality ground water, total dissolved solids is approximately 500 mg/L. USEPA (2018) documents the other relevant characteristics of these default waters.

Membrane Element

The WBS model includes the option of NF, low-pressure RO, or brackish water RO membrane elements, with a diameter of 4 inches, 8 inches, or 16 to 18 inches. (Not all manufacturers use the same size for their largest diameter elements, but the model is independent of the exact diameter.) Since not all NF membranes are effective for perchlorate treatment, the cost estimates below assume use of low-pressure RO membrane elements, consistent with the type of elements shown to be effective by Liang et al. (1998). For very small systems, the cost estimates use 4-inch diameter elements; above that point they use 8-inch elements. The switch from 4-inch to 8-inch elements takes place at about 75,000 gallons per day.

Recovery and Flux Rates

The WBS model takes target recovery and flux rates, and designs the reverse osmosis train to come as close as possible to them. The flux rate, in combination with the system design flow, determines the total membrane area in the system, and therefore the total number of membrane elements to be used. The recovery rate affects the number of membrane elements in series. For instance, two stages of seven elements each would give fourteen elements in series, while three stages of six elements each would give eighteen. To maintain adequate crossflow, each individual element is limited in the recovery it can achieve. Therefore, a higher recovery rate requires more elements in series.

In general, the cost estimates use recovery rates of 80 to 85 percent. At small flows, the small number of membrane elements limits flexibility in the system design; therefore, estimates up to about 500,000 gallons per day may use recovery rates as low as 70 percent.

Flux rates are based on the recommendations of various manufacturers for waters of different challenge. For ground water, the estimates use flux rates of 19 gfd. For surface water, the rates are 15 to 16 gfd.

Pretreatment

The RO model always includes 5-micron cartridge filters to protect the membrane elements from suspended solids. The cost estimates also include the addition of sulfuric acid and scale inhibitor to prevent fouling of the membrane elements.

The cost estimates include the addition of enough sulfuric acid to ensure that at least 1.5 mol/L of inorganic carbon is present in the RO permeate, to be available for alkalinity recovery; the resulting dose ranges from 16 to 45 mg/L.

While there are many scale inhibitors available, the model includes two general classes, which it calls basic antiscalant (to address calcium carbonate scaling) and premium antiscalant (to address sulfate salts and silica scaling). The cost estimates below include the addition of basic antiscalant. The antiscalant doses are sufficient to provide a dose of 15 mg/L in the concentrate,

assuming that all antiscalant is retained on the feed/concentrate side of the membrane. This requirement corresponds to a feed water dose from 2.25 to 4.5 mg/L.

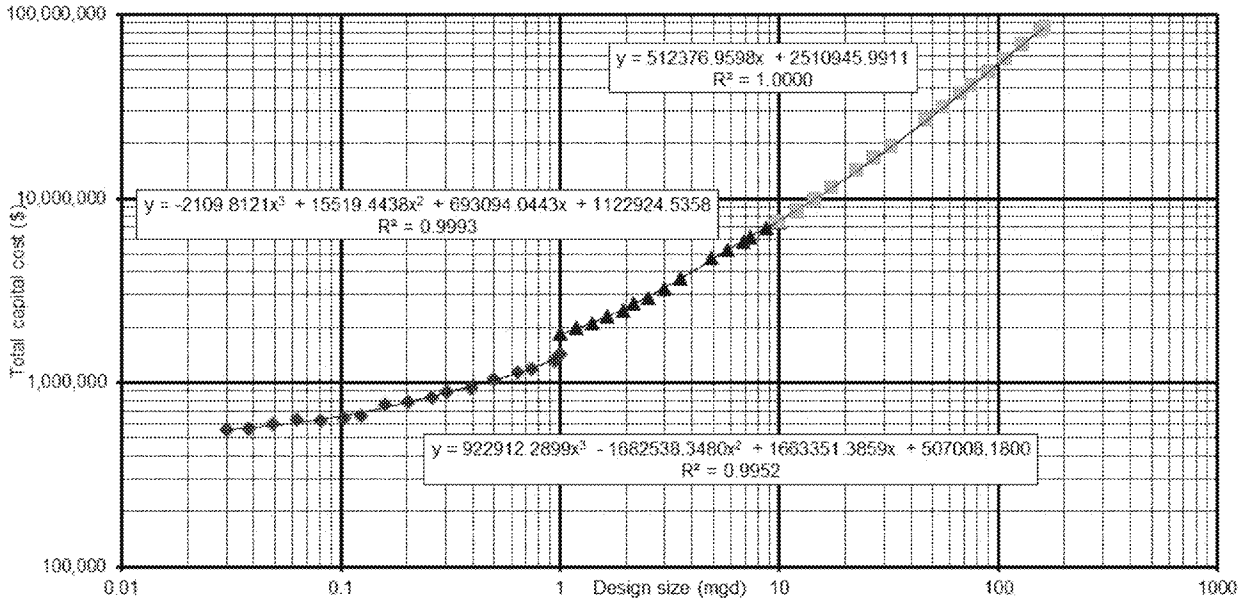
Residuals Discharge

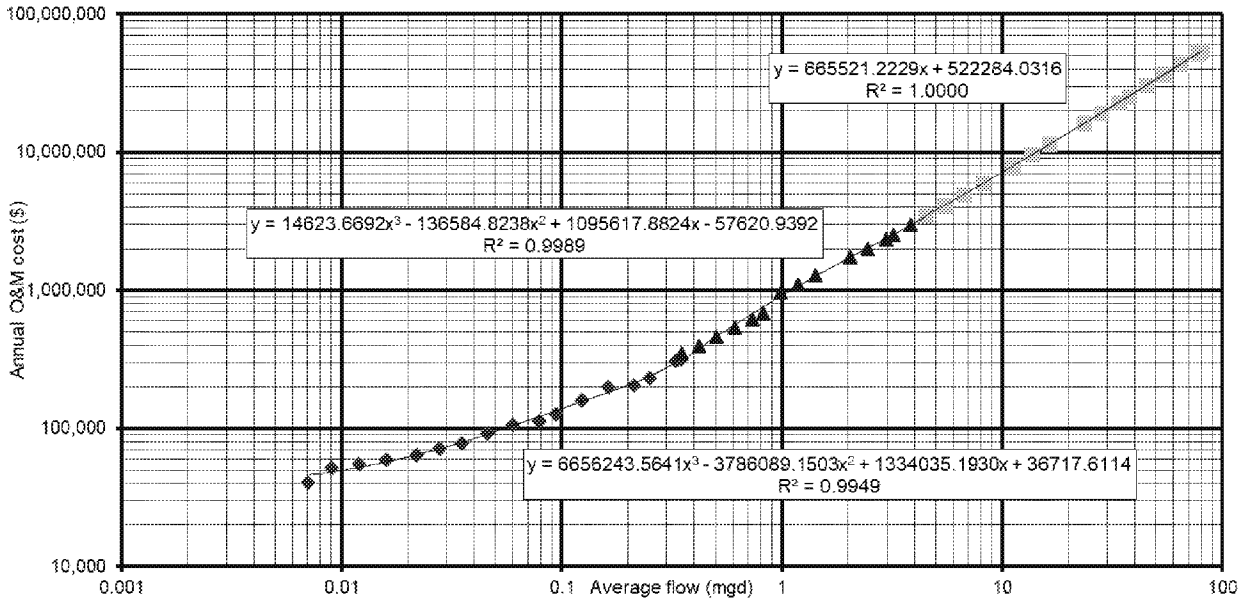
Residuals discharge is usually a major contributor to the cost of an RO facility. The RO/NF process generates two residuals streams: the membrane concentrate and spent cleaning solution. Since the spent cleaning solution is generated infrequently and in small amounts, the model assumes that it will be diluted and discharged with membrane concentrate. The cost estimates below assume the combined residuals are sent to a POTW. Although it might be impractical for most POTWs to treat very large concentrate flows, this scenario results in more conservative estimates (i.e., erring on the side of higher costs) than surface water (ocean) discharge or deep well injection.

7.4.2 Cost Estimates

The graphs below plot WBS cost model results in 2017 dollars at the mid cost level for removal of perchlorate from groundwater using RO (**[REF _Ref329598812 \h * MERGEFORMAT]**). Appendix B provides complete cost equations, including the high, mid, and low cost levels and for treatment of groundwater and surface water. Appendix C presents example WBS model outputs for selected flow rates, allowing review of individual cost line items.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Mid Cost Results for Removal of Perchlorate from Groundwater Using Reverse Osmosis (2017 dollars)





7.5 Costs for Point-of-use Technologies

7.5.1 Model Components and Assumptions

The document *Cost Evaluation of Point-of-Use and Point-of-Entry Treatment Units for Small Systems: Cost Estimating Tool and User Guide* (USEPA, 2007) provides a complete description of the WBS model for POU technologies. The POU model is capable of estimating equipment costs for a variety of POU devices, including POU RO devices and replacement filters. The POU model also includes the cost of the following other components of a complete POU program:

- POU RO device installation
- Public education program development
- POU device monitoring
- POU device maintenance.

Because only small systems would be expected to use POU programs, the POU model covers only the first four size categories shown in **[REF _Ref256672992 \h * MERGEFORMAT]**. Also, the POU model does not include assumptions or materials of construction that vary based on a "component level" or "cost level" input. Therefore, unlike the other models, it does not generate separate estimates for low-, mid-, and high-cost scenarios.

To use the POU model in estimating costs for perchlorate, EPA selected a program using RO devices. **[REF _Ref293040823 \h * MERGEFORMAT]** identifies the values used for parameters (other than equipment costs) that drive the costs of a POU RO program. EPA developed these assumptions based on EPA Guidance (USEPA, 2006b) and case study data, as discussed in detail in the paragraphs below.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. POU Model Assumptions for Perchlorate

Parameter Category	Value
Installation labor time	Plumber installation time: 2 hours per POU device (NSF, 2005) Scheduling time: 0.5 hours per household (USEPA, 2006b)
Public education program	Public meeting-related time: 20 hours Other outreach time (e.g., program updates in a billing mailer): 4 hours
Monitoring requirements	Initial monitoring for all units; annual monitoring for 1/3 of units (USEPA, 2006b) Sampling time: 0.25 hours per sampling event (NSF, 2005)
Filter replacement	Replacement schedule: RO element (3 years); post-RO carbon filter (1 year); pre-RO filters (9 months) (manufacturer recommendations) Filter replacement time: 0.5 hour per change-out (NSF, 2005) Scheduling time: 0.5 hours per household (USEPA, 2006b)

POU RO Device Installation

Installation of the POU RO devices will be the responsibility of the water system. The utility can, however, hire a licensed plumber or representative of the product manufacturer to install the devices. Based on the variety of plumbing issues encountered among older housing units in a

rural community, NSF (2005) recommends using an experienced plumber to perform the installations.

The POU model contains a default estimate of two hours per household to install the POU RO. A variety of factors such as existing plumbing conditions and travel distance will affect installation times across sites. The estimate is consistent with case study data. In a Grimes, California, arsenic demonstration program (NSF, 2005), POU adsorptive filter installation times ranged from 15 minutes to 3 hours depending on the accessibility of piping and the need for additional lines (e.g., to provide treated water to ice-makers). The mean device installation time was one hour, but total plumber billing records indicated that twice as much time was spent on all installation-related activities (e.g., additional time to obtain special plumbing fittings and return visits to homes when residents missed their appointments).

Installation costs also include administrative time for system staff to contact homeowners to schedule an installation appointment. EPA assumed an average of 30 minutes (0.5 hours) per household to schedule an appointment. Scheduling effort is likely to vary across customers, with some being relatively easy to schedule while others may require multiple calls to identify and contact the correct homeowners or to handle situations such as homeowner reluctance to participate or language barriers (USEPA, 2006b).

Public Education Program

EPA Guidance (2006b) recommends that systems implement a public education program to obtain and maintain customer participation and long-term customer satisfaction with the POU program. The two main program elements recommended in USEPA (2006b) are: public meetings prior to installing any POU devices to educate customers about the regulatory compliance requirements and the role of the POU devices; and POU program updates in billing mailers and on information flyers posted in public locations such as a post office, a public library, or a website. The POU model includes labor costs for the following program elements:

- preparing information for one public meeting
- attending the meeting
- preparing an additional billing mailer with program updates.

Public education program costs are not available from POU case studies. USEPA (2007) provides a detailed breakdown of the assumptions used to generate the time estimates shown in **[REF _Ref293040823 \h * MERGEFORMAT].** It also describes the costs for materials such as information flyers for the public meeting, meeting announcements, and billing mailers.

POU Device Monitoring

A system that implements a POU compliance strategy will need to monitor the quality of water produced by the treatment devices to demonstrate compliance with a perchlorate standard. The system will need to work with the appropriate regulatory agency to establish an approved compliance-monitoring schedule (USEPA, 2006b). The resulting monitoring schedule may have sampling rates in initial year that differ from sampling rates in subsequent years. EPA Guidance (2006b) provides an example of a monitoring schedule in which samples are taken from every unit during the first year to confirm that the units are working properly, and then monitoring

frequency declines to one-third of units each subsequent year. EPA's cost estimates incorporate these monitoring frequencies.

Monitoring costs include sampling time, shipping fees, and laboratory analysis fees. The average sampling is 15 minutes (0.25 hours). To minimize the burden on households as well as system resources, EPA assumes that sampling occurs during installation or maintenance trips. The assumption is consistent with the Grimes case study cost analysis (NSF, 2005) used an estimate of 15 minutes per sampling event.

POU Device Maintenance

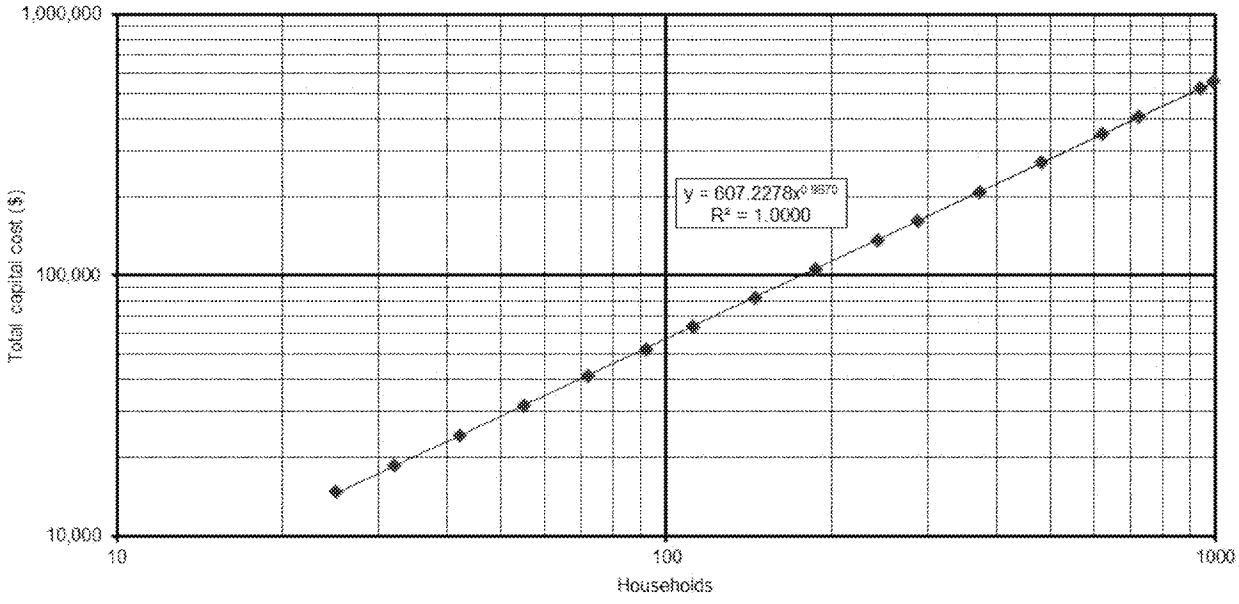
Maintenance for the POU RO device primarily includes replacing the four filters: RO membrane, two carbon filters, and the sediment filter. Replacement schedules reflect average useful lives based on vendor recommendations. On average, the RO membrane is replaced once every three years based on average replacement schedules across vendors, and the other filter cartridges are changed once per year.

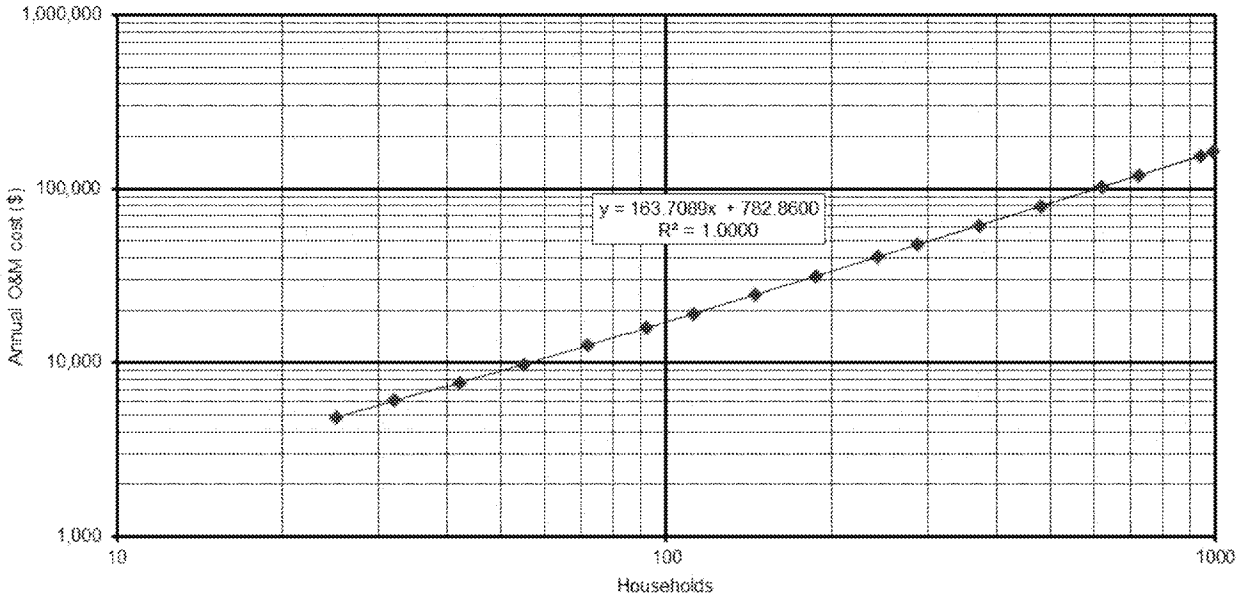
In addition to replacement filter costs, maintenance costs include scheduling time and time to change filters. The Grimes case study cost analysis (NSF, 2005) used an estimate of 15 minutes per filter change out. EPA assumed the average length of a maintenance call 30 minutes (0.5 hours) because the most frequent type of visit involves changing two filters. EPA used the same 30-minute scheduling time assumption that it used for initial installation.

7.5.2 Cost Estimates

[REF _Ref326065349 \h * MERGEFORMAT] plots WBS cost model results in 2017 dollars for removal of perchlorate from groundwater using POU treatment. Note that this exhibit is plotted based on the number of households served, rather than the system flow, because number of households is the more relevant parameter for POU treatment. EPA limits the POU model to a maximum of approximately 1,000 households served because implementing and maintaining a POU program for a greater number of households is likely to be impractical. Therefore, the exhibit does not extend beyond this maximum. As discussed above, the POU model also does not generate separate high, mid, and low cost estimates. Appendix B contains complete cost equations for POU treatment, including for groundwater and surface water. For use in national cost estimating, it also contains equations on the basis of design and average flow, in addition to those on the basis of households served. Appendix C presents example WBS model outputs for selected flow rates, allowing review of individual cost line items.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Cost Results for Removal of Perchlorate from Groundwater Using POU Treatment (2017 dollars)





7.6 Costs for Nontreatment Options

7.6.1 Overview

USEPA (2017c) provides a complete description of the engineering design process used by the WBS model for nontreatment options. The model can estimate costs for two nontreatment options: interconnection with another system and drilling a new well to replace a contaminated one. EPA based the model components, design parameters, and default user input values on information available for nontreatment case studies and cost analyses for prior regulations (USEPA, 1995; USEPA, 2006a; USEPA, 2006c; USEPA, 2008; AWWA, 2005; Lucey, 2008). These studies involved compliance via nontreatment options for contaminants such as arsenic, volatile organic contaminants, and radionuclides. The case studies are for systems that range in size from serving small communities with fewer than 100 connections to systems distributing 2.5 MGD. Although EPA does not have nontreatment case studies specific to perchlorate, the design and cost information contained in the case studies for other contaminants is transferable. Nontreatment options are less likely to be available for larger systems because of the quantity of water required. Therefore, EPA's WBS nontreatment cost model generates costs only for systems serving less than 10,000 people.

As discussed in Section [REF _Ref293044924 \r \h], the two options covered by the WBS nontreatment model (new wells or interconnection) are likely to have higher costs than other nontreatment options available for perchlorate. The sections below identify the specific cost elements included under each option. They also describe the specific inputs and assumptions that EPA used to generate the costs for each option in Section [REF _Ref293045245 \r \h]. For both options, the cost estimates assume that systems choosing a nontreatment option do so because they have an alternative source that will not require additional water treatment to address changes in raw water quality (i.e., no post-treatment). Because of this, they further assume no incremental waste or residuals management costs.

7.6.2 Model Components and Assumptions for New Wells

In addition to the common WBS direct capital cost items listed in **[REF _Ref256681355 \h * MERGEFORMAT]**, the WBS nontreatment model includes the following direct capital cost items specific to the new well option:

- Well casing, screens, and plugs
- Well installation costs including drilling, development, gravel pack, and surface seals
- Well pumps
- Piping (buried) and valves to connect the new well to the system.

It includes the following option-specific O&M elements:

- Operator labor for operating and maintaining well pumps and valves
- Materials for maintaining well pumps
- Energy for operating well pumps.

The option includes a small shed or other low cost building at the well site along with materials and labor for maintenance of this building. In calculating land costs, it incorporates a 100 foot buffer on all sides of the new well building to allow for a sanitary control area around the well,

as recommended in the peer review comments on the model. For new wells, the model includes all of the indirect capital costs shown in **[REF _Ref256681355 \h * MERGEFORMAT]**, except for yard piping. The paragraphs below describe specific inputs and assumptions used to generate costs for perchlorate under the new well nontreatment option.

Total Flow Rate Requirements and Flow per Well

As with other WBS models, design and average flow are inputs to the nontreatment model. In the case of nontreatment approaches, however, "design" flow is actually the peak flow required by the system, rather than the design capacity of a treatment plant. In the new well nontreatment option, the flow rate requirements determine the number of new wells required. The cost estimates below assume one new well would be installed per 500 gpm of water production capacity required.

Well Depth

Well depth will vary for each site depending on the geological formations and aquifer depths. Geophysical studies prior to well installation will provide guidance on optimum well depths. The model has pumps available to serve wells up to 1,350 feet in depth. The cost estimates below assume a 250-foot well depth. The estimates assume 50 percent of this depth is screened, allowing for sections of casing both above and below the well screen.

Pump Type

The size of the well will depend on the diameter of the pump used to draw water from the aquifer. The model contains three sizes of submersible pumps: 4-, 6-, and 8-inch diameter. Each size can serve a range of flows and depths, so the default size varies across system flows. The cost estimates below assume 4-inch pumps for systems in the smallest size category (25 to 100 people) and 6-inch pumps for larger systems.

Distance from Well to Distribution System

The distance between a new well and the distribution system affects pipe installation costs. No case studies provided distance information. The cost estimates below assume a default value of 500 feet.

7.6.3 Model Components and Assumptions for Interconnection

In addition to the common WBS direct capital cost items listed in **[REF _Ref256681355 \h * MERGEFORMAT]**, the WBS nontreatment model includes the following direct capital cost items specific to the interconnection option:

- Booster pumps or pressure reducing valves (depending on pressure at supply source)
- Concrete vaults (buried) for booster pumps or pressure reducing valves
- Interconnecting piping (buried) and valves.

It includes the following option-specific O&M elements:

- Cost of purchased water
- Operator labor for operating and maintaining booster pumps or pressure reducing valves (depending on pressure at supply source) and interconnecting valves

- Materials for maintaining booster pumps (if required by pressure at supply source)
- Energy for operating booster pumps (if required by pressure at supply source).

The option does not include any buildings. It includes all of the indirect capital costs shown in **[REF _Ref256681355 \h * MERGEFORMAT]**, except for yard piping, site work, and architectural fees. The paragraphs below describe specific inputs and assumptions used to generate costs for perchlorate under the interconnection nontreatment option.

Flow Rate Requirements

As with other WBS models, design and average flow are inputs to the nontreatment model. In the case of nontreatment approaches, however, "design" flow is actually the peak flow required by the system, rather than the design capacity of a treatment plant. In the interconnection nontreatment option, the flow rate requirements determine a number of system and equipment parameters, including pipeline and valve size and pump capacity and energy use (if required by pressure at the supply source).

Distance to Interconnection Water Supply

For utilities that have the ability to purchase water from a neighboring system, the capital cost of the interconnection project will depend on the distance between the two systems. If the systems are far apart geographically, the cost of installing a pipeline may be too high to make an interconnection project feasible. Also, a larger booster pump will be required to overcome friction losses along longer pipelines. The cost estimates below assume an average interconnection distance of 10,000 feet, based on comments from the peer review of the nontreatment model.

Pressure at Supply Water Source

The water pressure of purchased water may require adjustment prior to entering the purchasing system's distribution network (e.g., to account for elevation differences). If the wholesale supplier does not have enough pressure to meet the distribution needs of the interconnection project, then booster pumps are needed to move water from the supply source into the distribution system. The booster pump size is based on flow rate as well as distance and grade to the distribution system. If the supply source has more pressure than necessary then pressure reducing valves are needed. Based on comments from the peer review, the cost estimates below assume that differences in pressure between the supplier and the purchasing system are minimal, so that neither booster pumps nor pressure reducing valves are needed.

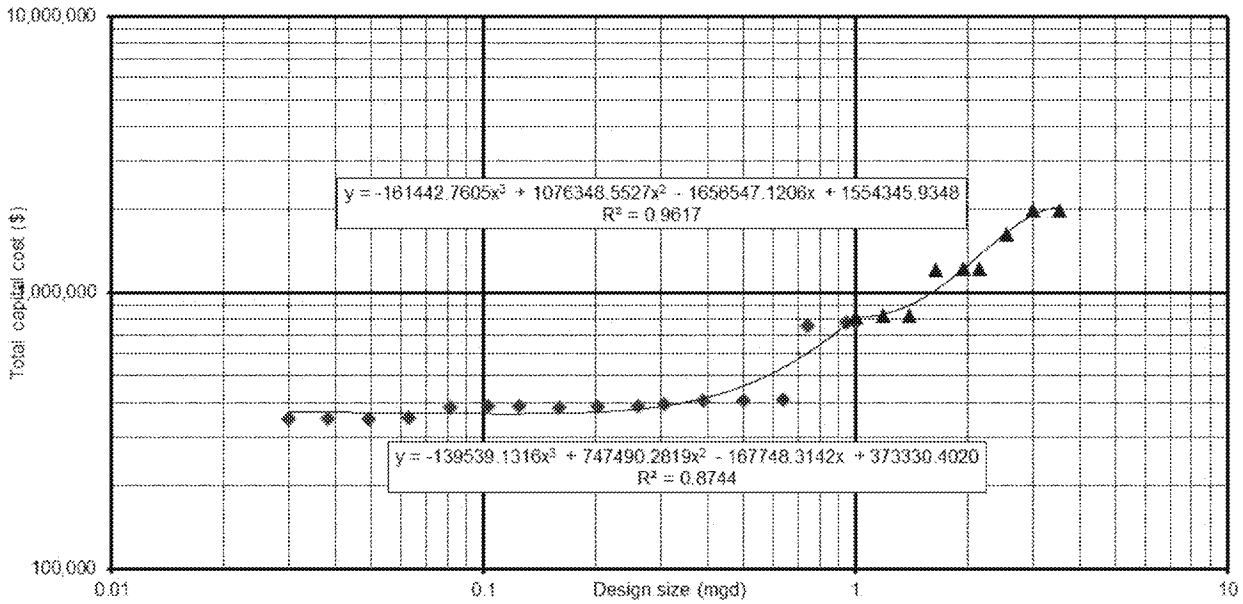
Cost of Purchased Water

An interconnection project will include one or more water rates paid to the wholesale system by the purchasing system. The model assumption is a single water rate for the average cost in dollars per thousand gallons of purchased water. Based on data in USEPA (2009), the mean revenue per thousand gallons among all wholesale systems is $1.85. The cost estimates below assume a higher cost of purchased water of $2.00 per thousand gallons, based on comments from the peer review.

7.6.4 Cost Estimates

The graphs below plot WBS cost model results in 2017 dollars at the mid cost level for the two nontreatment options for systems using groundwater: new wells (**[REF _Ref326066318 \h * MERGEFORMAT]**) and interconnection (**[REF _Ref326066329 \h * MERGEFORMAT]**). The exhibits do not extend beyond 3.536 MGD design flow, because the nontreatment model does not generate costs for larger systems. Appendix B provides complete cost equations for both nontreatment options, including the high, mid, and low cost levels and for interconnection of groundwater and surface water systems. Appendix C presents example WBS model outputs for selected flow rates, allowing review of individual cost line items.

Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Mid Cost Results for New Wells at Groundwater Systems (2017 dollars)



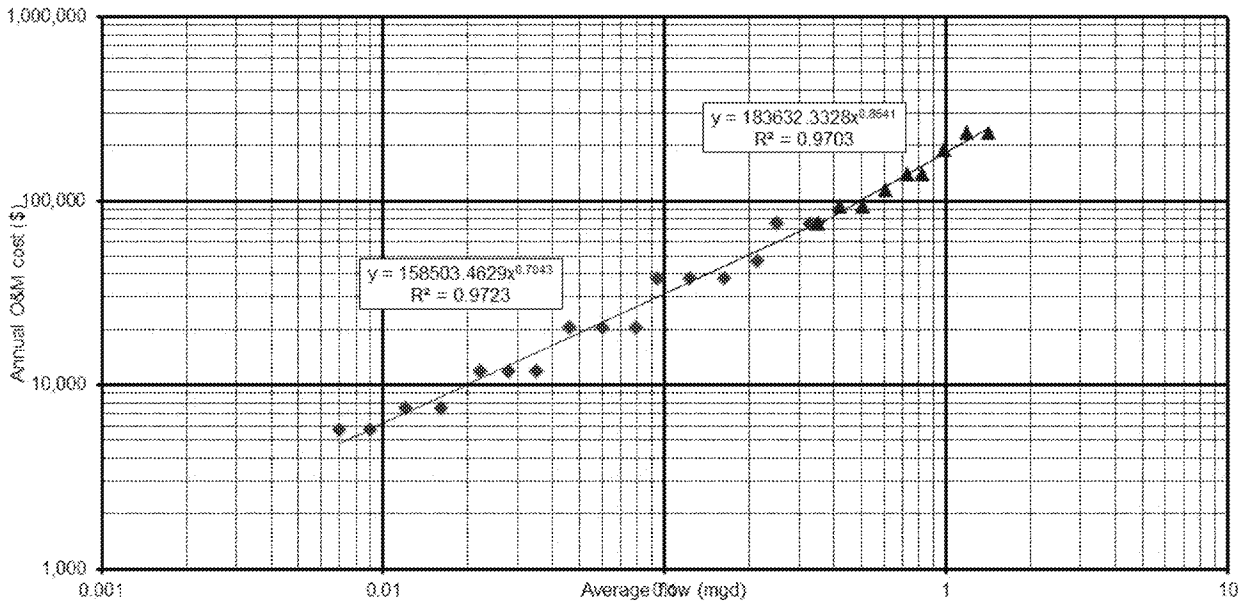
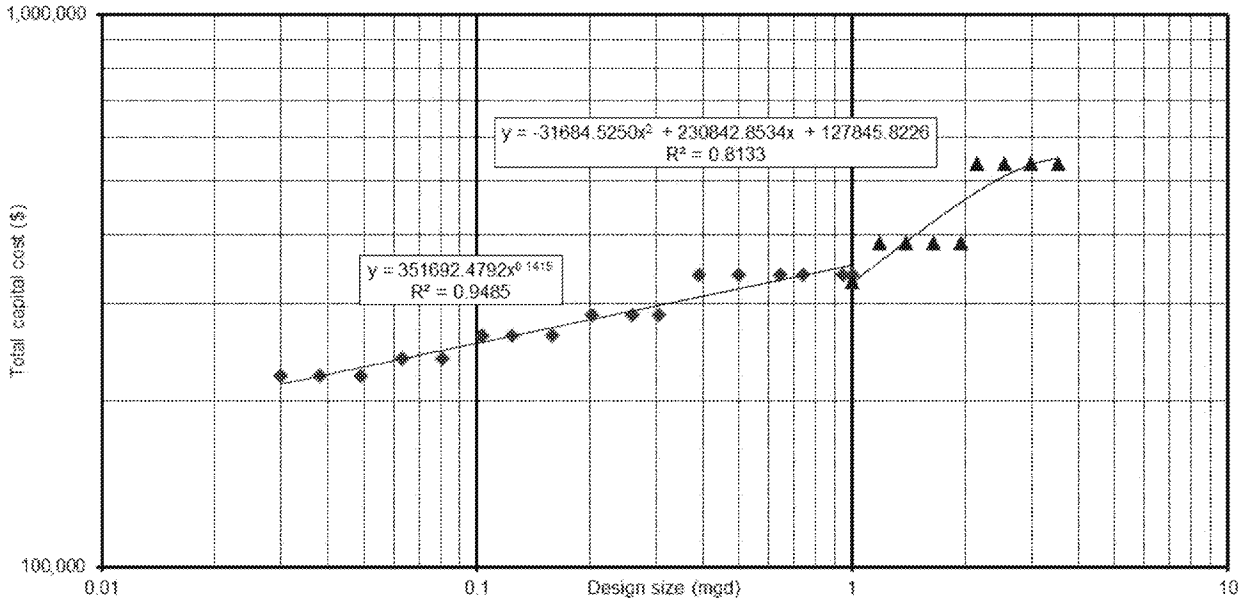
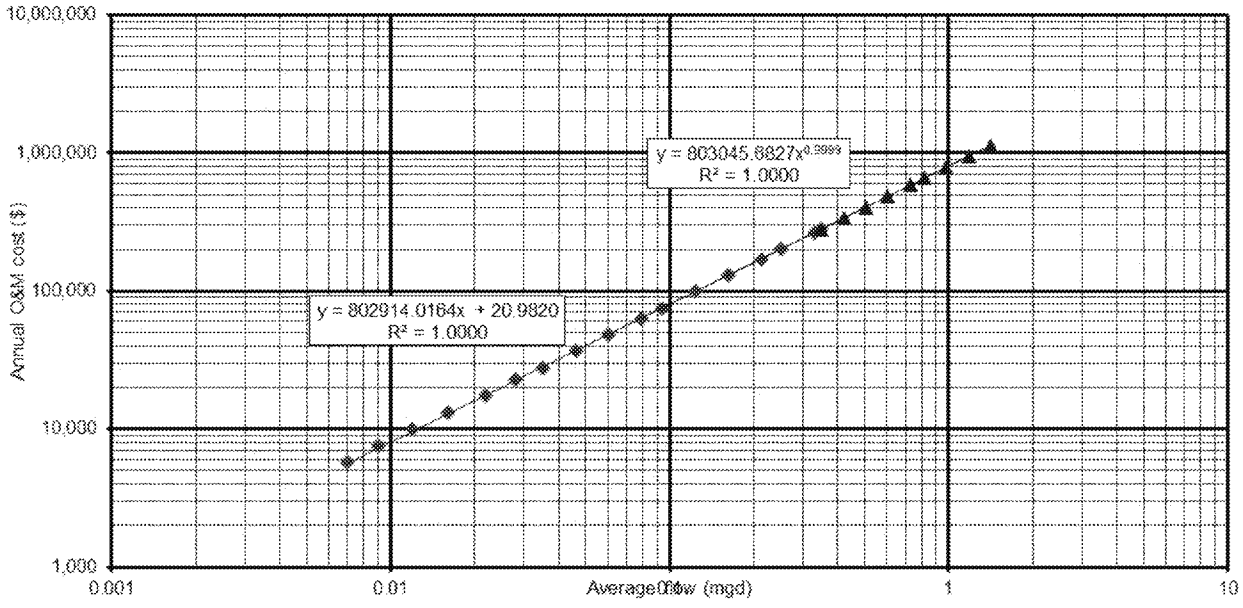


Exhibit [STYLEREF 1 \s]-[SEQ Exhibit * ARABIC \s 1]. Mid Cost Results for Interconnection of Groundwater Systems (2017 dollars)





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Appendix A: Residuals Treatment

For certain residuals from technologies removing perchlorate from drinking water, additional treatment may be desirable or required. Specifically, residuals from both ion exchange (see Chapter 2) and membrane technologies (see Chapter 4) may be amenable to treatment prior to their disposal, discharge, or reuse. One form of residuals treatment that has received considerable research attention uses biological treatment (see Chapter 3). Thus, the topic of residuals treatment is relevant to several of the technologies discussed in this document. Because of its cross-technology applicability, residuals treatment research is summarized here in an appendix.

Treatment technologies for residuals from technologies removing perchlorate from drinking water include biological treatment and physical/chemical reduction.[15] This appendix provides an overview of the status of each residuals treatment technology.

A.1 Biological Treatment of Residuals

Biological treatment of concentrated waste streams from ion exchange processes can be difficult due the microbial toxicity associated with the high salt content of the brine. In the case of an anion exchange process, the regeneration of the resin typically generates a 7 to 12 percent sodium hydroxide brine solution enriched in perchlorate. Gingras and Batista (2002) were unable to adapt a PRB culture to degrade perchlorate in an ion exchange brine. As little as 1 percent sodium hydroxide reduced perchlorate reduction rates by their perchlorate-degrading culture by half (Gingras and Batista, 2002). Batista et al. (2002) indicate that the use of halotolerant microbes that can reduce perchlorate in the presence of high levels of salinity would be required for effective biological brine treatment.

Pilot tests conducted by MWH and the University of Houston, however, evaluated biological treatment of spent brines with promising initial results. A biological system based on a marine sediment inoculum was shown to successfully and consistently remove perchlorate at concentrations of 1.5 to 3.0 mg/L from the brine to below 0.2 mg/L, the goal established for effective reuse of the brine. Investigators observed that as the treated brine was recycled to regenerate the exhausted ion exchange resin, the resin maintained its ability to remove perchlorate to less than 4 µg/L. After 30 reuse cycles, various constituents accumulated within the brine, including bicarbonate, sulfate, uranium, arsenic, chromium, fluoride, barium, and silica. These accumulated chemicals are site specific and depend upon raw water quality. Control of this accumulation through additional treatment might be required depending on site-specific concentrations. The researchers identified mixing and maintaining an anoxic environment as key operational requirements. Regular maintenance to remove scale build-up prevents system clogging. The researchers noted that the potential for precipitation and clogging is high under standard operating conditions (Case et al., 2004).

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[15] In addition, several sources (Boodoo, 2006; U.S. DoD, 2007; U.S. DoD, 2008a) present information on a potential treatment approach for spent caustic regenerant from an ion exchange system using weak-base resin. This approach uses a small, strong-base resin scavenger bed, with the spent resin from the scavenger bed ultimately disposed by incineration. Because study of this approach has been limited to weak-base resin regenerant, this appendix does not include further discussion of this residuals treatment method.

The literature does not include any detailed evaluation of the feasibility of biological treatment of spent tetrachloroferrate regenerant. Batista et al. (2002) suggest that such a system could be used if pH adjustment were applied to raise the pH of the regenerant. Recent studies of tetrachloroferrate regeneration (Gu et al., 2005; Lutes et al., 2010) do not include examination of biological treatment of spent regenerant.

Batista et al. (2000; 2002) have suggested that a primary advantage of weak-base resins is that caustic solutions used to regenerate these resins may be more amenable to biological treatment than conventional brine solutions. Instead of containing sodium chloride, which can be toxic to some microorganisms, these solutions could contain ammonium hydroxide, which can be used as a nutrient by microbes (Batista et al., 2000). On the other hand, the caustic solutions would require pH adjustment to lower the pH. Also, high levels of ammonium (greater than 0.3 percent) could be toxic to anaerobic biological systems. Ammonium might need to be air stripped or biologically oxidized to nitrate (Batista et al., 2002). Recent studies of regenerated weak-base resins (U.S. DoD, 2007 and 2008a) do not include examination of biological treatment of spent regenerant.

Xu et al. (2003) notes that the waste stream containing perchlorate produced from a RO process contains much lower amount of salts (less than 1 percent) than the sodium hydroxide brine generated using an ion exchange process. Giblin et al. (2002) inoculated a PBR with the pure culture perc1ace and tested its ability to remove perchlorate from a simulated RO rejectate. The researchers found that this system removed 98 percent of perchlorate from a twice-concentrated rejectate (total dissolved solids of 0.4 percent) with an influent perchlorate concentration of 8 mg/L and a residence time of 2 hours. The system removed nitrate simultaneously with perchlorate from an initial concentration as high as 900 mg/L to below 4 mg/L. Despite the efficiency of perchlorate removal, the system suffered from clogging due to precipitation of the high total dissolved solids of the twice-concentrated rejectate.

A.2 Physical/Chemical Reduction of Residuals

Calgon Carbon has developed a proprietary physical/chemical brine treatment system called the Perchlorate and Nitrate Destruction Module (PNDM). The PNDM is a high-pressure and high-temperature catalytic process that uses ammonia as a chemical reductant to reduce the nitrate and perchlorate in spent brine (MWH and University of Houston, 2003). In pilot tests that incorporated a nanofiltration unit to remove sulfate from the brine after PNDM treatment, Venkatesh et al. (2000) found that the PNDM system was able to reduce perchlorate in the spent brine from 60,000 to 70,000 µg/L to less than the detection limit of 125 µg/L. This reduction allowed reuse of the brine and reduced overall waste generation from 1.75 percent of water treated to 0.17 percent of water treated. The remaining waste consisted of the sulfate-laden reject from the nanofiltration step. With 70 mg/L chloride and 50 mg/L sulfate in this reject, the study suggests that blending with treated water is a feasible option (Venkatesh et al., 2000).

The pilot tests conducted by MWH and the University of Houston evaluated the PNDM system for treatment of spent brine from a conventional ion exchange configuration. The biological treatment initial results were promising. PNDM was able to reduce perchlorate in brine to below 0.2 mg/L and allowed reuse of the brine for up to 30 cycles (Case et al., 2004).

The MWH and University of Houston pilot tests also evaluated an electrolytic treatment process to reduce perchlorate in brine. This process, developed by Ionex for the treatment of nitrate contaminated water, is called IXL (MWH and University of Houston, 2003). Initial results, however, demonstrated minimal perchlorate reduction with this system (Case et al., 2004).

Applied Research Associates (ARA) has proposed an Integrated Thermal Treatment Process for treating spent brine. This process would concentrate the spent brine using reverse osmosis, thereby rejecting sulfate and nitrate salts, and concentrating the perchlorate. The concentrated perchlorate would then be thermally destroyed. The treated brine would be suitable for reuse and ARA estimates that the quantity of brine waste for disposal would be reduced by 95 to 99 percent. This thermal treatment approach, however, has been tested only in the laboratory for synthetic spent brine (ARA, 2000).

The Oak Ridge National Laboratory researchers have developed a proprietary methodology for reducing perchlorate in spent tetrachloroferrate regenerant solution. Reportedly, in this methodology, perchlorate decomposes into chloride under certain catalytic conditions within a few hours to one day with an initial perchlorate concentration of about 7,000 mg/L. The process does not otherwise alter the properties of the regenerant solution and allows it to be reused (Gu et al., 2003). More recently, Gu et al. (2005) reported on a process in which tetrachloroferrate regenerant is reduced with ferrous chloride in a thermoreactor. In this process, they observed perchlorate destruction efficiency of 92 to 97 percent, which enabled recycling of the spent regenerant. Lutes et al. (2010) further tested this process in a field-scale reactor and found perchlorate destruction efficiency from 73.6 to greater than 99.7 percent, a median efficiency of greater than 99.2 percent. The process has been patented and licensed exclusively to Calgon Carbon (Lutes et al., 2010).

Appendix B: Cost Equations

Notes:

- Cost equations presented here take one of the following forms, identified by which coefficients (C1 through C10) are nonzero:

$$\text{Cost} = C1\ Q^{C2}$$
$$\text{or} = C3\ \text{Ln}(Q) + C4$$
$$\text{or} = C5\ e^{(C6\ Q)}$$
$$\text{or} = C7\ Q^3 + C8\ Q^2 + C9\ Q + C10$$

  where Q is design flow in MGD for total capital costs, or average flow in MGD for annual O&M costs.

- Equations are designated as for small, medium, or large systems. These equations apply as follows:

  Small system equations apply where design flow (Q) is less than 1 MGD
  Medium system equations apply where design flow (Q) is 1 MGD or greater, but less than 10 MGD
  Large system equations apply where design flow (Q) is 10 MGD or greater

- For Point of Use/Point of Entry, alternative equations also are included where:

$$\text{Cost} = C1\ H^{C2}$$
$$\text{or} = C3\ \text{Ln}(H) + C4$$
$$\text{or} = C5\ e^{(C6\ H)}$$
$$\text{or} = C7\ H^3 + C8\ H^2 + C9\ H + C10$$

  where H is number of households served for both total capital costs and annual O&M costs.

- EPA developed each equation using the method described in Section [REF _Ref351026444 \r \h].

- Equations are derived from the following data files, with columns rearranged for ease of reference:

  - Results_Summary_GW_082817 for groundwater systems
  - Results_Summary_SW_082817 for surface water systems.

- For Anion Exchange for Perchlorate, the Perchlorate-selective 170,000 BV scenario corresponds to the Alternative resin (user defined) option in the source data files.

- For Point of Use/Point of Entry, costs do not vary by component level input (high, mid, low); equations are not presented for medium and large systems.

- For Non-treatment, medium system size curves are valid only up to 3.536 MGD design flow (1.417 MGD groundwater average flow and 1.345 MGD surface water average flow); equations are not presented for systems of greater size.

- For Non-treatment, equations are not presented for New Wells for surface water systems, because this option is not likely to be available for surface water systems.

B.1 Capital and O&M Cost Curve Parameters for Anion Exchange Treatment Scenarios

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Perchlorate-selective 250,000 BV	GW	Small	Low	Total Capital	0	0	0	0	0	0	165188.3006	-319172.535	472901.5875	81055.1941	17.74117647
Perchlorate-selective 250,000 BV	GW	Medium	Low	Total Capital	0	0	0	0	0	0	814.5718	-15685.9444	419749.9937	596924.4296	32.34
Perchlorate-selective 250,000 BV	GW	Large	Low	Total Capital	0	0	0	0	0	0	0	0	281010.0818	993827.2688	33.97647059
Perchlorate-selective 250,000 BV	GW	Small	Mid	Total Capital	0	0	0	0	0	0	111665.366	-213209.9	435508.3073	125329.6749	17.69411765
Perchlorate-selective 250,000 BV	GW	Medium	Mid	Total Capital	0	0	0	0	0	0	802.1603	-17543.4018	455922.7261	687296.3603	31.74
Perchlorate-selective 250,000 BV	GW	Large	Mid	Total Capital	0	0	0	0	0	0	0	0	287995.2658	1130875.789	33.95882353
Perchlorate-selective 250,000 BV	GW	Small	High	Total Capital	0	0	0	0	0	0	186840.2446	-375907.224	708990.975	171244.269	20.24705882
Perchlorate-selective 250,000 BV	GW	Medium	High	Total Capital	0	0	0	0	0	0	2804.3789	-52743.211	810631.6507	852108.8158	33.78
Perchlorate-selective 250,000 BV	GW	Large	High	Total Capital	0	0	0	0	0	0	0	0	444429.0529	1729726.784	34.71764706
Perchlorate-selective 250,000 BV	GW	Small	Low	Annual O&M	0	0	0	0	0	0	60323.2954	-52499.9905	95401.6475	4355.1619	17.74117647
Perchlorate-selective 250,000 BV	GW	Medium	Low	Annual O&M	0	0	0	0	0	0	0	-749.5103	107314.0049	25199.9683	32.34
Perchlorate-selective 250,000 BV	GW	Large	Low	Annual O&M	0	0	0	0	0	0	0	0	94348.8299	54918.7765	33.97647059
Perchlorate-selective 250,000 BV	GW	Small	Mid	Annual O&M	0	0	0	0	0	0	60323.2954	-52499.9905	95401.6475	4355.1619	17.69411765
Perchlorate-selective 250,000 BV	GW	Medium	Mid	Annual O&M	0	0	0	0	0	0	0	-793.0138	109785.9654	27443.6982	31.74
Perchlorate-selective 250,000 BV	GW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	0	94815.4066	50288.0306	33.95882353
Perchlorate-selective 250,000 BV	GW	Small	High	Annual O&M	0	0	0	0	0	0	0	-22144.6512	92551.7336	4510.6253	20.24705882
Perchlorate-selective 250,000 BV	GW	Medium	High	Annual O&M	0	0	0	0	0	0	0	-864.5234	111139.9758	27196.8415	33.78
Perchlorate-selective 250,000 BV	GW	Large	High	Annual O&M	0	0	0	0	0	0	0	27.2244	93568.467	64877.4787	34.71764706
Perchlorate-selective 170,000 BV	GW	Small	Low	Total Capital	0	0	0	0	0	0	165188.3006	-319172.535	472901.5875	81055.1941	17.74117647
Perchlorate-selective 170,000 BV	GW	Medium	Low	Total Capital	0	0	0	0	0	0	814.5718	-15685.9444	419749.9937	596924.4296	32.34

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Perchlorate-selective 170,000 BV	GW	Large	Low	Total Capital	0	0	0	0	0	0	0	0	281010.0818	993827.2688	33.97647059
Perchlorate-selective 170,000 BV	GW	Small	Mid	Total Capital	0	0	0	0	0	0	111665.366	-213209.9	435508.3073	125329.6749	17.69411765
Perchlorate-selective 170,000 BV	GW	Medium	Mid	Total Capital	0	0	0	0	0	0	802.1603	-17543.4018	455922.7261	687296.3603	31.74
Perchlorate-selective 170,000 BV	GW	Large	Mid	Total Capital	0	0	0	0	0	0	0	0	287995.2658	1130875.789	33.95882353
Perchlorate-selective 170,000 BV	GW	Small	High	Total Capital	0	0	0	0	0	0	186840.2446	-375907.224	708990.975	171244.269	20.24705882
Perchlorate-selective 170,000 BV	GW	Medium	High	Total Capital	0	0	0	0	0	0	2804.3789	-52743.211	810631.6507	852108.8158	33.78
Perchlorate-selective 170,000 BV	GW	Large	High	Total Capital	0	0	0	0	0	0	0	0	444429.0529	1729726.784	34.71764706
Perchlorate-selective 170,000 BV	GW	Small	Low	Annual O&M	0	0	0	0	0	0	56351.5026	-50187.5062	122627.1429	4364.8149	17.74117647
Perchlorate-selective 170,000 BV	GW	Medium	Low	Annual O&M	0	0	0	0	0	0	0	0	131580.5513	27443.0764	32.34
Perchlorate-selective 170,000 BV	GW	Large	Low	Annual O&M	0	0	0	0	0	0	0	0	122034.7577	53803.0803	33.97647059
Perchlorate-selective 170,000 BV	GW	Small	Mid	Annual O&M	0	0	0	0	0	0	56351.5026	-50187.5062	122627.1429	4364.8149	17.69411765
Perchlorate-selective 170,000 BV	GW	Medium	Mid	Annual O&M	0	0	0	0	0	0	0	0	133861.2533	29816.6188	31.74
Perchlorate-selective 170,000 BV	GW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	0	122526.36	48879.5863	33.95882353
Perchlorate-selective 170,000 BV	GW	Small	High	Annual O&M	0	0	0	0	0	0	57937.7322	-51428.4226	123700.2943	4441.0268	20.24705882
Perchlorate-selective 170,000 BV	GW	Medium	High	Annual O&M	0	0	0	0	0	0	-751.2236	4495.5752	128358.2051	31778.107	33.78
Perchlorate-selective 170,000 BV	GW	Large	High	Annual O&M	0	0	0	0	0	0	0	0	123508.7003	38942.7634	34.71764706
Perchlorate-selective 250,000 BV	SW	Small	Low	Total Capital	0	0	0	0	0	0	165274.688	-319329.202	472978.9565	81058.2965	17.74117647
Perchlorate-selective 250,000 BV	SW	Medium	Low	Total Capital	0	0	0	0	0	0	839.1878	-16075.29	421154.5885	595626.0307	32.34
Perchlorate-selective 250,000 BV	SW	Large	Low	Total Capital	0	0	0	0	0	0	0	0	280265.6113	1007900.297	33.98823529
Perchlorate-selective 250,000 BV	SW	Small	Mid	Total Capital	0	0	0	0	0	0	111750.4602	-213363.524	435584.8953	125332.7918	17.69411765
Perchlorate-selective 250,000 BV	SW	Medium	Mid	Total Capital	0	0	0	0	0	0	830.5377	-17999.3282	457555.6503	685792.943	31.74

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Perchlorate-selective 250,000 BV	SW	Large	Mid	Total Capital	0	0	0	0	0	0	0	0	287250.061	1144962.062	33.97058824
Perchlorate-selective 250,000 BV	SW	Small	High	Total Capital	0	0	0	0	0	0	186942.4138	-376095.796	709087.0242	171247.8793	20.24705882
Perchlorate-selective 250,000 BV	SW	Medium	High	Total Capital	0	0	0	0	0	0	2838.7252	-53286.93	812529.4756	850397.7787	33.78
Perchlorate-selective 250,000 BV	SW	Large	High	Total Capital	0	0	0	0	0	0	0	0	443634.4238	1743834.45	34.72941176
Perchlorate-selective 250,000 BV	SW	Small	Low	Annual O&M	0	0	0	0	0	0	0	-18741.0467	90566.6107	4395.0332	17.74117647
Perchlorate-selective 250,000 BV	SW	Medium	Low	Annual O&M	0	0	0	0	0	0	0	-598.7219	109065.4542	24276.2342	32.34
Perchlorate-selective 250,000 BV	SW	Large	Low	Annual O&M	0	0	0	0	0	0	0	0	95522.9118	71724.5663	33.98823529
Perchlorate-selective 250,000 BV	SW	Small	Mid	Annual O&M	0	0	0	0	0	0	0	-18741.0467	90566.6107	4395.0332	17.69411765
Perchlorate-selective 250,000 BV	SW	Medium	Mid	Annual O&M	0	0	0	0	0	0	0	0	109075.9181	28101.0967	31.74
Perchlorate-selective 250,000 BV	SW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	0	96019.7175	67473.7023	33.97058824
Perchlorate-selective 250,000 BV	SW	Small	High	Annual O&M	0	0	0	0	0	0	0	-19036.6668	91488.2917	4470.8681	20.24705882
Perchlorate-selective 250,000 BV	SW	Medium	High	Annual O&M	0	0	0	0	0	0	-1039.9695	6031.209	101107.6527	31206.5711	33.78
Perchlorate-selective 250,000 BV	SW	Large	High	Annual O&M	0	0	0	0	0	0	0	0	97012.5603	58878.3927	34.72941176
Perchlorate-selective 170,000 BV	SW	Small	Low	Total Capital	0	0	0	0	0	0	165274.688	-319329.202	472978.9565	81058.2965	17.74117647
Perchlorate-selective 170,000 BV	SW	Medium	Low	Total Capital	0	0	0	0	0	0	839.1878	-16075.29	421154.5885	595626.0307	32.34
Perchlorate-selective 170,000 BV	SW	Large	Low	Total Capital	0	0	0	0	0	0	0	0	280265.6113	1007900.297	33.98823529
Perchlorate-selective 170,000 BV	SW	Small	Mid	Total Capital	0	0	0	0	0	0	111750.4602	-213363.524	435584.8953	125332.7918	17.69411765
Perchlorate-selective 170,000 BV	SW	Medium	Mid	Total Capital	0	0	0	0	0	0	830.5377	-17999.3282	457555.6503	685792.943	31.74
Perchlorate-selective 170,000 BV	SW	Large	Mid	Total Capital	0	0	0	0	0	0	0	0	287250.061	1144962.062	33.97058824
Perchlorate-selective 170,000 BV	SW	Small	High	Total Capital	0	0	0	0	0	0	186942.4138	-376095.796	709087.0242	171247.8793	20.24705882
Perchlorate-selective 170,000 BV	SW	Medium	High	Total Capital	0	0	0	0	0	0	2838.7252	-53286.93	812529.4756	850397.7787	33.78

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Perchlorate-selective 170,000 BV	SW	Large	High	Total Capital	0	0	0	0	0	0	0	0	443634.4238	1743834.45	34.72941176
Perchlorate-selective 170,000 BV	SW	Small	Low	Annual O&M	0	0	0	0	0	0	0	-18636.7959	118095.4167	4401.0983	17.74117647
Perchlorate-selective 170,000 BV	SW	Medium	Low	Annual O&M	0	0	0	0	0	0	0	-594.8003	136645.3404	24283.6711	32.34
Perchlorate-selective 170,000 BV	SW	Large	Low	Annual O&M	0	0	0	0	0	0	0	0	123198.8697	70820.6621	33.98823529
Perchlorate-selective 170,000 BV	SW	Small	Mid	Annual O&M	0	0	0	0	0	0	0	-18636.7959	118095.4167	4401.0983	17.69411765
Perchlorate-selective 170,000 BV	SW	Medium	Mid	Annual O&M	0	0	0	0	0	0	0	0	136673.7625	28097.7332	31.74
Perchlorate-selective 170,000 BV	SW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	0	123719.8582	66316.3849	33.97058824
Perchlorate-selective 170,000 BV	SW	Small	High	Annual O&M	0	0	0	0	0	0	0	-18919.6285	119009.5802	4477.345	20.24705882
Perchlorate-selective 170,000 BV	SW	Medium	High	Annual O&M	0	0	0	0	0	0	-1038.7155	6027.6327	128706.7892	31207.6465	33.78
Perchlorate-selective 170,000 BV	SW	Large	High	Annual O&M	0	0	0	0	0	0	0	0	124761.0668	57213.3622	34.72941176

Cost = C1 * Q ^ C2 + C3 * Ln(Q) + C4 + C5 * Exp (C6 * Q) + C7 * Q^3 + C8 * Q^2 + C9 * Q + C10
Where Q is design flow in MGD for total capital costs and average flow in MGD for annual O&M costs

B.2 Capital and O&M Cost Curve Parameters for Biological Treatment Scenarios

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Fixed Bed Pressure Vessel	GW	Small	Low	Total Capital	0	0	0	0	0	0	360664.2489	-719515.71	1107604.628	643541.8543	24.46470588
Fixed Bed Pressure Vessel	GW	Medium	Low	Total Capital	0	0	0	0	0	0	-1230.8188	4236.7079	740451.7857	1652605.61	31.79333333
Fixed Bed Pressure Vessel	GW	Large	Low	Total Capital	0	0	0	0	0	0	0	-33.3723	558954.1451	2437567.235	31.31764706
Fixed Bed Pressure Vessel	GW	Small	Mid	Total Capital	0	0	0	0	0	0	492476.6413	-1025849.33	1436856.86	715106.4333	23.12941176
Fixed Bed Pressure Vessel	GW	Medium	Mid	Total Capital	0	0	0	0	0	0	0	-15229.9667	887780.101	1850883.189	31.34
Fixed Bed Pressure Vessel	GW	Large	Mid	Total Capital	0	0	0	0	0	0	0	0	564980.0264	3622086.493	31.35882353
Fixed Bed Pressure Vessel	GW	Small	High	Total Capital	0	0	0	0	0	0	770133.6573	-1683703.84	2371838.543	836853.9079	25.47647059
Fixed Bed Pressure Vessel	GW	Medium	High	Total Capital	0	0	0	0	0	0	-2465.7652	13844.2369	1241563.686	2576024.887	33.52
Fixed Bed Pressure Vessel	GW	Large	High	Total Capital	0	0	0	0	0	0	7.225	-1535.1083	1011253.121	3406280.863	33.12352941
Fixed Bed Pressure Vessel	GW	Small	Low	Annual O&M	0	0	0	0	0	0	0	-45961.3314	158156.0739	27926.5161	24.46470588
Fixed Bed Pressure Vessel	GW	Medium	Low	Annual O&M	0	0	0	0	0	0	1184.1123	-14333.9198	180043.52	62255.524	31.79333333
Fixed Bed Pressure Vessel	GW	Large	Low	Annual O&M	0	0	0	0	0	0	0	0	126538.9848	104543.6316	31.31764706
Fixed Bed Pressure Vessel	GW	Small	Mid	Annual O&M	0	0	0	0	0	0	0	-76492.4588	176417.3995	27695.5647	23.12941176

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Fixed Bed Pressure Vessel	GW	Medium	Mid	Annual O&M	0	0	0	0	0	0	0	-6827.1527	173032.9405	75031.6456	31.34
Fixed Bed Pressure Vessel	GW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	0	129201.3891	88438.183	31.35882353
Fixed Bed Pressure Vessel	GW	Small	High	Annual O&M	0	0	0	0	0	0	91643.6805	-120401.753	185483.6022	28225.6213	25.47647059
Fixed Bed Pressure Vessel	GW	Medium	High	Annual O&M	0	0	0	0	0	0	0	-7136.1131	175890.2434	75595.8595	33.52
Fixed Bed Pressure Vessel	GW	Large	High	Annual O&M	0	0	0	0	0	0	-2.6058	349.0829	122625.9002	143270.435	33.12352941
Fixed Bed Gravity Basin	GW	Small	Low	Total Capital	0	0	0	0	0	0	-199338.503	108033.2323	1102079.756	943520.528	28.67058824
Fixed Bed Gravity Basin	GW	Medium	Low	Total Capital	2610057.586	0.5365	0	0	0	0	0	0	0	0	32.84
Fixed Bed Gravity Basin	GW	Large	Low	Total Capital	0	0	0	0	0	0	0	0	369737.988	7037405.771	31.62352941
Fixed Bed Gravity Basin	GW	Small	Mid	Total Capital	0	0	0	0	0	0	0	-243851.42	1460419.766	1052522.957	27.42941176
Fixed Bed Gravity Basin	GW	Medium	Mid	Total Capital	2931011.596	0.534	0	0	0	0	0	0	0	0	32.36666667
Fixed Bed Gravity Basin	GW	Large	Mid	Total Capital	0	0	0	0	0	0	0	-142.8363	409982.8163	7189477.16	31.61764706
Fixed Bed Gravity Basin	GW	Small	High	Total Capital	0	0	0	0	0	0	202978.9468	-743201.86	2218774.508	1232771.998	29.86470588
Fixed Bed Gravity Basin	GW	Medium	High	Total Capital	3735296.534	0.5134	0	0	0	0	0	0	0	0	33.99333333
Fixed Bed Gravity Basin	GW	Large	High	Total Capital	0	0	0	0	0	0	0	-127.9367	472526.5562	9035136.284	32.77058824

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Fixed Bed Gravity Basin	GW	Small	Low	Annual O&M	0	0	0	0	0	0	-244584.565	45607.9876	217316.197	33588.7142	28.67058824
Fixed Bed Gravity Basin	GW	Medium	Low	Annual O&M	0	0	0	0	0	0	0	-6559.4032	186687.2639	75555.8157	32.84
Fixed Bed Gravity Basin	GW	Large	Low	Annual O&M	0	0	0	0	0	0	0	0	118304.6266	225492.918	31.62352941
Fixed Bed Gravity Basin	GW	Small	Mid	Annual O&M	0	0	0	0	0	0	-185910.722	21574.4589	226502.4065	35193.5095	27.42941176
Fixed Bed Gravity Basin	GW	Medium	Mid	Annual O&M	0	0	0	0	0	0	0	-7143.548	194111.8555	77654.2262	32.36666667
Fixed Bed Gravity Basin	GW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	0	120590.8015	210480.3335	31.61764706
Fixed Bed Gravity Basin	GW	Small	High	Annual O&M	0	0	0	0	0	0	0	-76893.7765	246083.0756	36218.5012	29.86470588
Fixed Bed Gravity Basin	GW	Medium	High	Annual O&M	0	0	0	0	0	0	0	-7101.1547	196805.7999	79557.3458	33.99333333
Fixed Bed Gravity Basin	GW	Large	High	Annual O&M	0	0	0	0	0	0	-1.6021	227.8999	115719.1797	264822.2223	32.77058824
Fluidized Bed Pressure Vessel	GW	Small	Low	Total Capital	0	0	0	0	0	0	-165867.923	-28166.6787	1025869.936	861046.6691	27.07647059
Fluidized Bed Pressure Vessel	GW	Medium	Low	Total Capital	0	0	0	0	0	0	-1758.0291	18962.1919	649400.0564	1694269.883	31.5
Fluidized Bed Pressure Vessel	GW	Large	Low	Total Capital	0	0	0	0	0	0	0	-184.9186	540273.6829	2881509.567	30.98823529
Fluidized Bed	GW	Small	Mid	Total Capital	0	0	0	0	0	0	0	-362080.784	1369255.056	997173.1712	25.97058824

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Pressure Vessel															
Fluidized Bed Pressure Vessel	GW	Medium	Mid	Total Capital	0	0	0	0	0	0	-1020.4755	5469.6152	807095.7564	1937384.124	31
Fluidized Bed Pressure Vessel	GW	Large	Mid	Total Capital	0	0	0	0	0	0	0	-199.5054	571178.1483	3627131.011	30.94705882
Fluidized Bed Pressure Vessel	GW	Small	High	Total Capital	0	0	0	0	0	0	0	-575922.439	2258409.846	1191761.253	28.81764706
Fluidized Bed Pressure Vessel	GW	Medium	High	Total Capital	0	0	0	0	0	0	-2245.5247	23231.221	1173986.54	2689612.461	33.32
Fluidized Bed Pressure Vessel	GW	Large	High	Total Capital	0	0	0	0	0	0	2.0713	-750.9524	958369.9281	4502384.894	33.18823529
Fluidized Bed Pressure Vessel	GW	Small	Low	Annual O&M	0	0	0	0	0	0	0	-61439.932	156677.6914	37218.503	27.07647059
Fluidized Bed Pressure Vessel	GW	Medium	Low	Annual O&M	0	0	0	0	0	0	0	-4273.302	151726.0086	77431.6855	31.5
Fluidized Bed Pressure Vessel	GW	Large	Low	Annual O&M	0	0	0	0	0	0	0	0	118931.5849	156492.319	30.98823529
Fluidized Bed Pressure Vessel	GW	Small	Mid	Annual O&M	0	0	0	0	0	0	0	-66125.2755	165892.0237	42644.1251	25.97058824
Fluidized Bed Pressure Vessel	GW	Medium	Mid	Annual O&M	0	0	0	0	0	0	0	-4768.8748	158659.8589	83835.7669	31

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Fluidized Bed Pressure Vessel	GW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	0	121214.2539	142830.8114	30.94705882
Fluidized Bed Pressure Vessel	GW	Small	High	Annual O&M	0	0	0	0	0	0	0	-69019.5329	173487.8271	46943.947	28.81764706
Fluidized Bed Pressure Vessel	GW	Medium	High	Annual O&M	0	0	0	0	0	0	0	-5090.8845	161873.9793	83364.5317	33.32
Fluidized Bed Pressure Vessel	GW	Large	High	Annual O&M	0	0	0	0	0	0	0	0	125753.2694	116080.0404	33.18823529
Fixed Bed Pressure Vessel	SW	Small	Low	Total Capital	0	0	0	0	0	0	376530.23	-743505.873	1116042.748	643296.522	24.46470588
Fixed Bed Pressure Vessel	SW	Medium	Low	Total Capital	0	0	0	0	0	0	-1306.1553	5435.3388	734513.1972	1657773.704	31.79333333
Fixed Bed Pressure Vessel	SW	Large	Low	Total Capital	0	0	0	0	0	0	-1.3562	301.9828	536580.3031	2719357.571	31.31764706
Fixed Bed Pressure Vessel	SW	Small	Mid	Total Capital	0	0	0	0	0	0	376530.23	-743505.873	1116042.748	643296.522	24.46470588
Fixed Bed Pressure Vessel	SW	Medium	Mid	Total Capital	0	0	0	0	0	0	-1306.1553	5435.3388	734513.1972	1657773.704	31.79333333
Fixed Bed Pressure Vessel	SW	Large	Mid	Total Capital	0	0	0	0	0	0	-1.3562	301.9828	536580.3031	2719357.571	31.31764706
Fixed Bed Pressure Vessel	SW	Small	High	Total Capital	0	0	0	0	0	0	787557.8629	-1711551.3	2382625.539	836532.0821	25.47647059
Fixed Bed Pressure Vessel	SW	Medium	High	Total Capital	0	0	0	0	0	0	-2509.418	14699.0305	1235969.914	2580751.403	33.52

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Fixed Bed Pressure Vessel	SW	Large	High	Total Capital	0	0	0	0	0	0	7.2587	-1541.3548	1010264.132	3400477.674	33.11764706
Fixed Bed Pressure Vessel	SW	Small	Low	Annual O&M	0	0	0	0	0	0	0	-30006.0913	151948.7891	27786.4856	24.46470588
Fixed Bed Pressure Vessel	SW	Medium	Low	Annual O&M	0	0	0	0	0	0	0	-6472.2083	171959.0723	65214.7013	31.79333333
Fixed Bed Pressure Vessel	SW	Large	Low	Annual O&M	0	0	0	0	0	0	0	-50.0737	133952.7487	116880.3955	31.31764706
Fixed Bed Pressure Vessel	SW	Small	Mid	Annual O&M	0	0	0	0	0	0	0	-47426.4264	167113.6865	27582.7544	23.11764706
Fixed Bed Pressure Vessel	SW	Medium	Mid	Annual O&M	0	0	0	0	0	0	0	-7571.6831	182100.1207	70400.4121	31.33333333
Fixed Bed Pressure Vessel	SW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	-48.638	136680.3001	104187.003	31.35882353
Fixed Bed Pressure Vessel	SW	Small	High	Annual O&M	0	0	0	0	0	0	0	-54988.4534	172649.2074	28155.967	25.47647059
Fixed Bed Pressure Vessel	SW	Medium	High	Annual O&M	0	0	0	0	0	0	0	-7944.4304	185272.3046	70814.7398	33.52
Fixed Bed Pressure Vessel	SW	Large	High	Annual O&M	0	0	0	0	0	0	0	-47.6434	142797.7639	76278.2943	33.11764706
Fixed Bed Gravity Basin	SW	Small	Low	Total Capital	0	0	0	0	0	0	-194555.784	103163.0231	1100879.375	944940.1123	28.66470588
Fixed Bed Gravity Basin	SW	Medium	Low	Total Capital	2611597.865	0.5352	0	0	0	0	0	0	0	0	32.84
Fixed Bed Gravity Basin	SW	Large	Low	Total Capital	0	0	0	0	0	0	0	-97.4647	385856.916	6442653.679	31.6
Fixed Bed Gravity Basin	SW	Small	Mid	Total Capital	0	0	0	0	0	0	0	-241076.609	1455779.615	1054413.219	27.42941176

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Fixed Bed Gravity Basin	SW	Medium	Mid	Total Capital	2932533.852	0.5325	0	0	0	0	0	0	0	0	32.36666667
Fixed Bed Gravity Basin	SW	Large	Mid	Total Capital	0	0	0	0	0	0	1.4957	-485.1302	428334.3343	6915717.611	31.59411765
Fixed Bed Gravity Basin	SW	Small	High	Total Capital	0	0	0	0	0	0	0	-437897.61	2100725.869	1242829.494	29.86470588
Fixed Bed Gravity Basin	SW	Medium	High	Total Capital	3737297.463	0.5121	0	0	0	0	0	0	0	0	33.98666667
Fixed Bed Gravity Basin	SW	Large	High	Total Capital	0	0	0	0	0	0	-2.2055	429.0556	433942.163	9481048.78	32.74117647
Fixed Bed Gravity Basin	SW	Small	Low	Annual O&M	0	0	0	0	0	0	-295094.821	107422.9682	200339.6042	33528.7699	28.66470588
Fixed Bed Gravity Basin	SW	Medium	Low	Annual O&M	0	0	0	0	0	0	0	-7078.7184	196694.4742	70481.3509	32.84
Fixed Bed Gravity Basin	SW	Large	Low	Annual O&M	0	0	0	0	0	0	0	-53.1455	125332.4549	225578.8415	31.6
Fixed Bed Gravity Basin	SW	Small	Mid	Annual O&M	0	0	0	0	0	0	0	-39781.1639	225091.591	34770.0602	27.42941176
Fixed Bed Gravity Basin	SW	Medium	Mid	Annual O&M	0	0	0	0	0	0	0	-7922.9458	205415.3033	71952.8472	32.36666667
Fixed Bed Gravity Basin	SW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	-49.281	127203.5984	221133.0458	31.59411765
Fixed Bed Gravity Basin	SW	Small	High	Annual O&M	0	0	0	0	0	0	-265504.07	96891.6626	214451.7462	36419.1032	29.86470588
Fixed Bed Gravity Basin	SW	Medium	High	Annual O&M	0	0	0	0	0	0	0	-7678.6964	207592.0873	74095.0996	33.98666667
Fixed Bed Gravity Basin	SW	Large	High	Annual O&M	0	0	0	0	0	0	0	0	127770.6593	245595.9535	32.74117647

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Fluidized Bed Pressure Vessel	SW	Small	Low	Total Capital	0	0	0	0	0	0	-175859.574	-15604.5734	1022532.417	861605.1699	27.08235294
Fluidized Bed Pressure Vessel	SW	Medium	Low	Total Capital	0	0	0	0	0	0	-1853.4978	20390.6304	642914.6996	1699906.968	31.5
Fluidized Bed Pressure Vessel	SW	Large	Low	Total Capital	0	0	0	0	0	0	0	-184.3819	539381.2799	2877427.798	30.99411765
Fluidized Bed Pressure Vessel	SW	Small	Mid	Total Capital	0	0	0	0	0	0	97225.5085	-508869.031	1424987.278	993856.3133	25.97647059
Fluidized Bed Pressure Vessel	SW	Medium	Mid	Total Capital	0	0	0	0	0	0	0	-11461.5583	883976.9293	1850411.667	30.99333333
Fluidized Bed Pressure Vessel	SW	Large	Mid	Total Capital	0	0	0	0	0	0	0	-197.1765	569947.5394	3626369.958	30.95294118
Fluidized Bed Pressure Vessel	SW	Small	High	Total Capital	0	0	0	0	0	0	0	-579364.841	2261637.972	1192128.15	28.81764706
Fluidized Bed Pressure Vessel	SW	Medium	High	Total Capital	0	0	0	0	0	0	-2497.6049	26750.0461	1159072.431	2703008.262	33.32
Fluidized Bed Pressure Vessel	SW	Large	High	Total Capital	0	0	0	0	0	0	0	-236.2879	924354.1605	4920097.242	33.19411765
Fluidized Bed Pressure Vessel	SW	Small	Low	Annual O&M	0	0	0	0	0	0	0	-48119.3527	151722.3833	37060.3885	27.08235294
Fluidized Bed	SW	Medium	Low	Annual O&M	0	0	0	0	0	0	683.1623	-8992.2086	166147.0816	70692.5368	31.5

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Pressure Vessel															
Fluidized Bed Pressure Vessel	SW	Large	Low	Annual O&M	0	0	0	0	0	0	0	-77.7363	127503.5199	136708.2479	30.99411765
Fluidized Bed Pressure Vessel	SW	Small	Mid	Annual O&M	0	0	0	0	0	0	0	-51241.3715	160339.9151	42473.2257	25.97647059
Fluidized Bed Pressure Vessel	SW	Medium	Mid	Annual O&M	0	0	0	0	0	0	0	-5128.5574	165688.954	80177.5823	30.99333333
Fluidized Bed Pressure Vessel	SW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	-76.4289	129834.5381	126303.1959	30.95294118
Fluidized Bed Pressure Vessel	SW	Small	High	Annual O&M	0	0	0	0	0	0	0	-52938.0151	167468.4034	46763.9136	28.81764706
Fluidized Bed Pressure Vessel	SW	Medium	High	Annual O&M	0	0	0	0	0	0	0	-5503.3764	169209.2828	79563.3081	33.32
Fluidized Bed Pressure Vessel	SW	Large	High	Annual O&M	0	0	0	0	0	0	0	-69.7757	134187.4415	107314.9692	33.19411765

Cost = C1 * Q ^ C2 + C3 * Ln(Q) + C4 + C5 * Exp (C6 * Q) + C7 * Q^3 + C8 * Q^2 + C9 * Q + C10
Where Q is design flow in MGD for total capital costs and average flow in MGD for annual O&M costs

B.3 Capital and O&M Cost Curve Parameters for Reverse Osmosis Treatment Scenarios

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
High Qual GW	GW	Small	Low	Total Capital	0	0	0	0	0	0	419730.7281	-788209.698	1051419.014	442510.3593	24.25882353
High Qual GW	GW	Medium	Low	Total Capital	0	0	0	0	0	0	-2786.1614	27165.9297	609019.2816	834956.3855	30.08666667
High Qual GW	GW	Large	Low	Total Capital	0	0	0	0	0	0	0	0	501464.6241	2255690.684	29.34117647
High Qual GW	GW	Small	Mid	Total Capital	0	0	0	0	0	0	922912.2899	-1682538.35	1663351.386	507008.18	21.88823529
High Qual GW	GW	Medium	Mid	Total Capital	0	0	0	0	0	0	-2109.8121	15519.4438	693094.0443	1122924.536	28.22
High Qual GW	GW	Large	Mid	Total Capital	0	0	0	0	0	0	0	0	512376.9598	2510945.991	29.54705882
High Qual GW	GW	Small	High	Total Capital	0	0	0	0	0	0	766189.679	-1380227.98	1525573.733	570809.2307	24.37058824
High Qual GW	GW	Medium	High	Total Capital	0	0	0	0	0	0	-2107.3138	14031.7866	729255.4764	1165183.835	29.69333333
High Qual GW	GW	Large	High	Total Capital	0	0	0	0	0	0	0	43.302	528875.1103	2776676.683	29.88823529
High Qual GW	GW	Small	Low	Annual O&M	0	0	0	0	0	0	6656243.564	-3786089.15	1334035.193	36717.6114	24.25882353
High Qual GW	GW	Medium	Low	Annual O&M	0	0	0	0	0	0	14623.6692	-136584.824	1095617.882	-57620.9392	30.08666667
High Qual GW	GW	Large	Low	Annual O&M	0	0	0	0	0	0	0	0	665521.2229	522284.0316	29.34117647
High Qual GW	GW	Small	Mid	Annual O&M	0	0	0	0	0	0	6656243.564	-3786089.15	1334035.193	36717.6114	21.88823529
High Qual GW	GW	Medium	Mid	Annual O&M	0	0	0	0	0	0	14623.6692	-136584.824	1095617.882	-57620.9392	28.22
High Qual GW	GW	Large	Mid	Annual O&M	0	0	0	0	0	0	0	0	665521.2229	522284.0316	29.54705882
High Qual GW	GW	Small	High	Annual O&M	0	0	0	0	0	0	6656243.564	-3786089.15	1334035.193	36717.6114	24.37058824
High Qual GW	GW	Medium	High	Annual O&M	0	0	0	0	0	0	14623.6692	-136584.824	1095617.882	-57620.9392	29.69333333
High Qual GW	GW	Large	High	Annual O&M	0	0	0	0	0	0	0	0	665521.2229	522284.0316	29.88823529
High Qual SW	SW	Small	Low	Total Capital	0	0	0	0	0	0	149193.1749	-494226.186	1100191.755	425799.664	24.38235294
High Qual SW	SW	Medium	Low	Total Capital	0	0	0	0	0	0	0	-20031.7053	832358.7573	712738.9352	30.41333333

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
High Qual SW	SW	Large	Low	Total Capital	0	0	0	0	0	0	0	0	471323.5873	2660282.067	30.1
High Qual SW	SW	Small	Mid	Total Capital	0	0	0	0	0	0	710187.6349	-1479543.01	1773005.169	482742.038	22.09411765
High Qual SW	SW	Medium	Mid	Total Capital	0	0	0	0	0	0	992.0306	-36548.5993	935963.6527	986641.0663	28.54666667
High Qual SW	SW	Large	Mid	Total Capital	0	0	0	0	0	0	0	0	482545.7284	2941963.972	30.31764706
High Qual SW	SW	Small	High	Total Capital	0	0	0	0	0	0	521778.1744	-1165763.6	1665430.871	535877.9142	24.41764706
High Qual SW	SW	Medium	High	Total Capital	0	0	0	0	0	0	0	-22177.6296	904905.0085	1106566.125	30.02666667
High Qual SW	SW	Large	High	Total Capital	0	0	0	0	0	0	0	0	506185.1909	3060324.078	30.66470588
High Qual SW	SW	Small	Low	Annual O&M	0	0	0	0	0	0	6589736.981	-3985129.69	1508433.457	36750.2247	24.38235294
High Qual SW	SW	Medium	Low	Annual O&M	0	0	0	0	0	0	57128.2822	-406859.935	1486200.795	-119209.519	30.41333333
High Qual SW	SW	Large	Low	Annual O&M	0	0	0	0	0	0	11.5056	-1617.309	643746.394	390169.1403	30.1
High Qual SW	SW	Small	Mid	Annual O&M	0	0	0	0	0	0	6589736.981	-3985129.69	1508433.457	36750.2247	22.09411765
High Qual SW	SW	Medium	Mid	Annual O&M	0	0	0	0	0	0	57128.2822	-406859.935	1486200.795	-119209.519	28.54666667
High Qual SW	SW	Large	Mid	Annual O&M	0	0	0	0	0	0	11.5056	-1617.309	643746.394	390169.1403	30.31764706
High Qual SW	SW	Small	High	Annual O&M	0	0	0	0	0	0	6589736.981	-3985129.69	1508433.457	36750.2247	24.41764706
High Qual SW	SW	Medium	High	Annual O&M	0	0	0	0	0	0	57128.2822	-406859.935	1486200.795	-119209.519	30.02666667
High Qual SW	SW	Large	High	Annual O&M	0	0	0	0	0	0	11.5056	-1617.309	643746.394	390169.1403	30.66470588

Cost = C1 * Q ^ C2 + C3 * Ln(Q) + C4 + C5 * Exp (C6 * Q) + C7 * Q^3 + C8 * Q^2 + C9 * Q + C10
Where Q is design flow in MGD for total capital costs and average flow in MGD for annual O&M costs

B.4 Capital and O&M Cost Curve Parameters for Point-of-Use Treatment Scenarios (Flow Basis)

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
POU Reverse Osmosis	GW	Small	n/a	Total Capital	552638.6724	1.0352	0	0	0	0	0	0	0	0	10
POU Reverse Osmosis	GW	Small	n/a	Annual O&M	0	0	0	0	0	0	0	-99260.9973	496421.4345	1775.6587	10
POU Reverse Osmosis	SW	Small	n/a	Total Capital	555487.2438	1.0462	0	0	0	0	0	0	0	0	10
POU Reverse Osmosis	SW	Small	n/a	Annual O&M	0	0	0	0	0	0	0	0	460080.1825	688.6075	10

Cost = C1 * Q ^ C2 + C3 * Ln(Q) + C4 + C5 * Exp (C6 * Q) + C7 * Q^3 + C8 * Q^2 + C9 * Q + C10
Where Q is design flow in MGD for total capital costs and average flow in MGD for annual O&M costs

B.5 Capital and O&M Cost Curve Parameters for Point-of-Use Treatment Scenarios (Household Basis)

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
POU Reverse Osmosis	GW	Small	n/a	Total Capital	607.2278	0.987	0	0	0	0	0	0	0	0	10
POU Reverse Osmosis	GW	Small	n/a	Annual O&M	0	0	0	0	0	0	0	0	163.7089	782.86	10
POU Reverse Osmosis	SW	Small	n/a	Total Capital	608.0877	0.9868	0	0	0	0	0	0	0	0	10
POU Reverse Osmosis	SW	Small	n/a	Annual O&M	0	0	0	0	0	0	0	0	163.7627	788.7267	10

Cost = C1 * H ^ C2 + C3 * Ln(H) + C4 + C5 * Exp (C6 * H) + C7 * H^3 + C8 * H^2 + C9 * H + C10
Where H is number of households served

B.6 Capital and O&M Cost Curve Parameters for Non-Treatment Scenarios

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
Interconnection	GW	Small	Low	Total Capital	338077.9484	0.1356	0	0	0	0	0	0	0	0	17
Interconnection	GW	Medium	Low	Total Capital	0	0	0	0	0	0	0	-31084.5197	227314.1808	118001.2476	21.98888889
Interconnection	GW	Small	Mid	Total Capital	351692.4792	0.1415	0	0	0	0	0	0	0	0	16.92941176
Interconnection	GW	Medium	Mid	Total Capital	0	0	0	0	0	0	0	-31684.525	230842.8534	127845.8226	21.74444444
Interconnection	GW	Small	High	Total Capital	353452.9305	0.1363	0	0	0	0	0	0	0	0	17
Interconnection	GW	Medium	High	Total Capital	0	0	0	0	0	0	0	-32984.1112	240477.5383	121870.7095	21.9
Interconnection	GW	Small	Low	Annual O&M	0	0	0	0	0	0	0	0	802914.0164	20.982	17
Interconnection	GW	Medium	Low	Annual O&M	803045.6827	0.9999	0	0	0	0	0	0	0	0	21.98888889
Interconnection	GW	Small	Mid	Annual O&M	0	0	0	0	0	0	0	0	802914.0164	20.982	16.92941176
Interconnection	GW	Medium	Mid	Annual O&M	803045.6827	0.9999	0	0	0	0	0	0	0	0	21.74444444
Interconnection	GW	Small	High	Annual O&M	0	0	0	0	0	0	0	0	802914.0164	20.982	17
Interconnection	GW	Medium	High	Annual O&M	803045.6827	0.9999	0	0	0	0	0	0	0	0	21.9
New Well Construction	GW	Small	Low	Total Capital	0	0	0	0	0	0	0	293739.0823	-56575.0209	187426.9077	17.1
New Well Construction	GW	Medium	Low	Total Capital	0	0	0	0	0	0	0	-7446.9958	329941.3709	82930.8255	22.41111111
New Well Construction	GW	Small	Mid	Total Capital	0	0	0	0	0	0	-139539.132	747490.2819	-167748.314	373330.402	33.86470588
New Well Construction	GW	Medium	Mid	Total Capital	0	0	0	0	0	0	-161442.761	1076348.553	-1656547.12	1554345.935	39.21111111
New Well Construction	GW	Small	High	Total Capital	0	0	0	0	0	0	-186326.987	850714.244	-198767.813	384792.9094	34.31764706
New Well Construction	GW	Medium	High	Total Capital	0	0	0	0	0	0	-170156.492	1136151.351	-1756631.22	1640223.951	39.38888889
New Well Construction	GW	Small	Low	Annual O&M	158503.4629	0.7043	0	0	0	0	0	0	0	0	17.1
New Well Construction	GW	Medium	Low	Annual O&M	183632.3328	0.8641	0	0	0	0	0	0	0	0	22.41111111

Design	GW/ SW	Size Category	Comp Level	Cost Type	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Useful Life
New Well Construction	GW	Small	Mid	Annual O&M	158503.4629	0.7043	0	0	0	0	0	0	0	0	33.86470588
New Well Construction	GW	Medium	Mid	Annual O&M	183632.3328	0.8641	0	0	0	0	0	0	0	0	39.21111111
New Well Construction	GW	Small	High	Annual O&M	158503.4629	0.7043	0	0	0	0	0	0	0	0	34.31764706
New Well Construction	GW	Medium	High	Annual O&M	183632.3328	0.8641	0	0	0	0	0	0	0	0	39.38888889
Interconnection	SW	Small	Low	Total Capital	338077.9484	0.1356	0	0	0	0	0	0	0	0	17
Interconnection	SW	Medium	Low	Total Capital	0	0	0	0	0	0	0	-31084.5197	227314.1808	118001.2476	21.98888889
Interconnection	SW	Small	Mid	Total Capital	351692.4792	0.1415	0	0	0	0	0	0	0	0	16.92941176
Interconnection	SW	Medium	Mid	Total Capital	0	0	0	0	0	0	0	-31684.525	230842.8534	127845.8226	21.74444444
Interconnection	SW	Small	High	Total Capital	353452.9305	0.1363	0	0	0	0	0	0	0	0	17
Interconnection	SW	Medium	High	Total Capital	0	0	0	0	0	0	0	-32984.1112	240477.5383	121870.7095	21.9
Interconnection	SW	Small	Low	Annual O&M	0	0	0	0	0	0	0	0	802695.4	116.2102	17
Interconnection	SW	Medium	Low	Annual O&M	803045.4022	0.9999	0	0	0	0	0	0	0	0	21.98888889
Interconnection	SW	Small	Mid	Annual O&M	0	0	0	0	0	0	0	0	802695.4	116.2102	16.92941176
Interconnection	SW	Medium	Mid	Annual O&M	803045.4022	0.9999	0	0	0	0	0	0	0	0	21.74444444
Interconnection	SW	Small	High	Annual O&M	0	0	0	0	0	0	0	0	802695.4	116.2102	17
Interconnection	SW	Medium	High	Annual O&M	803045.4022	0.9999	0	0	0	0	0	0	0	0	21.9

Cost = C1 * Q ^ C2 + C3 * Ln(Q) + C4 + C5 * Exp (C6 * Q) + C7 * Q^3 + C8 * Q^2 + C9 * Q + C10
Where Q is design flow in MGD for total capital costs and average flow in MGD for annual O&M costs

Appendix C: Example WBS Model Outputs

Notes:

- Example outputs presented here correspond to treatment of groundwater.
- To show the variations among both system size and cost level, the examples chosen for each scenario modeled typically include a low cost small system, a mid cost medium system, and a high cost large system.
- Each of the examples is among the individual flow rate-specific estimates used to generate the cost equations presented in Appendix B (see Section [REF _Ref351114655 \r \h] for details on the method used to develop the equation).

Anion Exchange for Perchlorate, design 0.500 mgd, average 0.162 mgd, Low-Cost Components, Resin type: Perchlorate-selective 250,000 BV

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1	Pressure Vessels - Carbon Steel - Plastic Internals	35,590	30
2.1	Ion Exchange Resin - Perchlorate-selective	40,858	N/A
3.4.1	Caustic Storage Tanks - Plastic/XLPE	844	7
3.4.2	Caustic Storage Tanks - Heat Tracing	1,454	7
3.4.3	Caustic Storage Tanks - Insulation	163	7
4.1	Cartridge Filters - Cartridge Filters	24,784	30
5.1.1	Backwash Piping - PVC	205	17
5.3.1	Process Piping - PVC	311	17
5.5.1	Inlet and Outlet Piping - PVC	311	17
5.7.1	Caustic Piping - PVC	60	17
5.8.1	Residuals Piping - PVC	198	17
5.8.2	Residuals Piping - Excavation	1,064	17
5.8.3	Residuals Piping - Bedding	61	17
5.8.4	Residuals Piping - Backfill and Compaction	493	17
5.8.5	Residuals Piping - Thrust Blocks	96	17
6.1.1	Valves and Fittings - Motor/Air Operated (on/off) - Process - Polypropylene/PVC	9,580	20
6.1.2	Valves and Fittings - Motor/Air Operated (on/off) - Backwash - Polypropylene/PVC	4,218	20
6.2.1	Valves and Fittings - Manual - Inlet and outlet - Polypropylene/PVC	1,282	20
6.2.2	Valves and Fittings - Manual - Process - Polypropylene/PVC	1,282	20
6.3.2	Valves and Fittings - Check Valves - Inlet and Outlet - Polypropylene/PVC	2,705	20
6.3.7	Valves and Fittings - Check Valves - Residuals - Polypropylene/PVC	243	20
8.2.1	Mixers for Caustic Storage Tanks - Mounted	1,656	22
11.1.1	Instrumentation and Controls - Flow Meters - Inlet and Outlet - Propeller	4,141	14
11.3.1	Instrumentation and Controls - Flow Meters - Backwash - Propeller	3,227	14
11.4.1	Instrumentation and Controls - Flow Meters - Residuals - Propeller	2,625	14
11.9	Instrumentation and Controls - High/Low Alarm (for caustic tanks)	593	14
11.12	Instrumentation and Controls - Head loss sensors	4,242	14
11.13.1	Instrumentation and Controls - Sampling Ports - Stainless Steel	250	30
12.1.1	System Controls - PLC Units - PLC racks/power supplies	340	8
12.1.2	System Controls - PLC Units - CPUs	1,256	8
12.1.3	System Controls - PLC Units - I/O discrete input modules	307	8
12.1.4	System Controls - PLC Units - I/O discrete output modules	375	8
12.1.5	System Controls - PLC Units - I/O combination analog modules	1,958	8
12.1.6	System Controls - PLC Units - Ethernet modules	1,730	8
12.1.9	System Controls - PLC Units - UPSs	563	8
12.2.1	System Controls - Operator Equipment - Drive controllers	1,072	14
12.2.2	System Controls - Operator Equipment - Operator interface units	3,911	8
13.1.1	Building Structures and HVAC - Building 1 - Small Low Cost Shed	11,961	20
13.3	Building Structures and HVAC - Concrete Pad	2,592	37
Indirect	Indirect and Add-On Costs (contingency from model)	96,284	20
	Process Cost	**168,600**	
	System Cost	**264,884**	
	O&M Cost	**18,351**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Construction Management	4,102
Process Engineering	33,720
Site Work	3,332
Yard Piping	2,810
Geotechnical	0
Standby Power	0
Electrical (including yard wiring)	15,405
Mobilization and Demobilization	0
Architectural Fees for Treatment Building	0
Permits	24
Pilot Study	15,573
Land Cost	1,086
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Contingency (0.0%)	0
Miscellaneous Allowance (10.0%)	16,860
Legal, Fiscal, and Administrative (2.0%)	3,372
Sales Tax (0.0%)	0
Financing during Construction (0.0%)	0

Breakdown of O&M costs	Annual Cost ($/year)
Manager (8 hrs/yr @ $45.2396/hr)	371
Clerical (8 hrs/yr @ $30.4776/hr)	250
Operator (82 hrs/yr @ $31.9149/hr)	2,616
Cartridge filter replacement (7 filters/yr @ $191.6015/sf/yr)	1,380
Facility maintenance (materials and labor) (260 sf @ $5.7866/sf/yr)	1,505
Sodium Hydroxide - Small Qty (5268 lbs/yr @ $0.302/lb)	1,591
Perchlorate-selective (32 cf/yr @ $256.5165/cf)	8,111
Energy for backwash/rinse pumps (0 Mwh/yr @ $0.1212/kwh)	0
Energy for lighting (0 Mwh/yr @ $0.1212/kwh)	3
Energy for ventilation (0 Mwh/yr @ $0.1212/kwh)	7
POTW discharge fees (953 gal/yr @ $0.3881/gal)	370
Spent resin disposal (1 ton/yr @ $697.6744/ton)	474
Spent cartridge filter disposal (0 ton/yr @ $74.9152/ton)	6
Miscellaneous Allowance (0 @ $)	1,668

Anion Exchange for Perchlorate, design 5.809 mgd, average 2.455 mgd, Mid-Cost Components, Resin type: Perchlorate-selective 250,000 BV

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1	Pressure Vessels - Carbon Steel - Plastic Internals	264,172	35
2.1	Ion Exchange Resin - Perchlorate-selective	487,390	N/A
3.1.1	Backwash/Rinse Tanks - Fiberglass	11,822	25
3.4.1	Caustic Storage Tanks - Fiberglass	5,578	10
3.4.2	Caustic Storage Tanks - Heat Tracing	1,573	10
3.4.3	Caustic Storage Tanks - Insulation	947	10
3.5.1	Caustic Day Tanks - Fiberglass	4,749	10
3.5.2	Caustic Day Tanks - Heat Tracing	1,455	10
3.5.3	Caustic Day Tanks - Insulation	182	10
4.1	Cartridge Filters - Cartridge Filters	166,640	35
5.1.1	Backwash Piping - CPVC	7,502	22
5.3.1	Process Piping - CPVC	9,549	22
5.5.1	Inlet and Outlet Piping - CPVC	19,446	22
5.7.1	Caustic Piping - CPVC	1,119	22
5.8.1	Residuals Piping - CPVC	2,590	22
5.8.2	Residuals Piping - Excavation	1,187	22
5.8.3	Residuals Piping - Bedding	70	22
5.8.4	Residuals Piping - Backfill and Compaction	550	22
5.8.5	Residuals Piping - Thrust Blocks	409	22
6.1.1	Valves and Fittings - Motor/Air Operated (on/off) - Process - Cast Iron	53,747	25
6.1.2	Valves and Fittings - Motor/Air Operated (on/off) - Backwash - Cast Iron	44,639	25
6.1.6	Valves and Fittings - Motor/Air Operated (on/off) - Caustic - Stainless Steel	2,072	25
6.2.1	Valves and Fittings - Manual - Inlet and outlet - Cast Iron	5,215	25
6.2.2	Valves and Fittings - Manual - Process - Cast Iron	11,357	25
6.3.1	Valves and Fittings - Check Valves - Backwash - Cast Iron	3,857	25
6.3.2	Valves and Fittings - Check Valves - Inlet and Outlet - Cast Iron	10,467	25
6.3.7	Valves and Fittings - Check Valves - Residuals - Cast Iron	1,082	25
7.1	Pumps - Booster	69,732	20
7.2	Pumps - Backwash/Rinse	23,885	20
8.2.1	Mixers for Caustic Storage Tanks - Mounted	1,802	25
8.3.1	Mixers for Caustic Day Tanks - Mounted	1,658	25
11.1.1	Instrumentation and Controls - Flow Meters - Inlet and Outlet - Venturi	17,176	15
11.3.1	Instrumentation and Controls - Flow Meters - Backwash - Venturi	12,496	15
11.4.1	Instrumentation and Controls - Flow Meters - Residuals - Venturi	9,686	15
11.6	Instrumentation and Controls - High/Low Alarm (for backwash tanks)	593	15
11.9	Instrumentation and Controls - High/Low Alarm (for caustic tanks)	1,185	15
11.11	Instrumentation and Controls - Temperature meters	593	15
11.12	Instrumentation and Controls - Head loss sensors	23,332	15
11.13.1	Instrumentation and Controls - Sampling Ports - Carbon Steel	500	25
11.17	Instrumentation and Controls - Turbidity meters	5,223	15
12.1.1	System Controls - PLC Units - PLC racks/power supplies	680	10
12.1.2	System Controls - PLC Units - CPUs	1,256	10
12.1.3	System Controls - PLC Units - I/O discrete input modules	614	10
12.1.4	System Controls - PLC Units - I/O discrete output modules	375	10
12.1.5	System Controls - PLC Units - I/O combination analog modules	5,221	10
12.1.6	System Controls - PLC Units - Ethernet modules	1,730	10
12.1.7	System Controls - PLC Units - Base expansion modules	118	10
12.1.8	System Controls - PLC Units - Base expansion controller modules	86	10
12.1.9	System Controls - PLC Units - UPSs	563	10
12.2.1	System Controls - Operator Equipment - Drive controllers	6,435	15
12.2.2	System Controls - Operator Equipment - Operator interface units	920	10
12.2.3	System Controls - Operator Equipment - PC Workstations	1,006	10
12.2.4	System Controls - Operator Equipment - Printers - laser jet	627	10

WBS #	Item	Total Cost ($)	Useful Life (yrs)
12.2.5	System Controls - Operator Equipment - Printers - dot matrix	642	10
12.3.1	System Controls - Controls Software - Operator interface software	366	10
12.3.2	System Controls - Controls Software - PLC programming software	474	10
12.3.3	System Controls - Controls Software - PLC data collection software	690	10
12.3.4	System Controls - Controls Software - Plant intelligence software	11,480	10
13.1.1	Building Structures and HVAC - Building 1 - Medium Quality	390,703	40
13.1.3.1	Building Structures and HVAC - Building 1 - Heating and Cooling System - Heat pump	5,957	25
13.3	Building Structures and HVAC - Concrete Pad	53,134	40
Indirect	Indirect and Add-On Costs (contingency from model)	1,073,196	40
	Process Cost	**1,770,308**	
	System Cost	**2,843,504**	
	O&M Cost	**284,473**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Construction Management	115,738
Process Engineering	212,437
Site Work	60,232
Yard Piping	26,287
Geotechnical	0
Standby Power	21,078
Electrical (including yard wiring)	132,051
Mobilization and Demobilization	87,480
Architectural Fees for Treatment Building	35,984
Permits	24
Pilot Study	69,717
Land Cost	11,216
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Contingency (0.0%)	0
Miscellaneous Allowance (10.0%)	177,031
Legal, Fiscal, and Administrative (2.0%)	35,406
Sales Tax (0.0%)	0
Financing during Construction (5.0%)	88,515

Breakdown of O&M costs	Annual Cost ($/year)
Manager (47 hrs/yr @ $57.6375/hr)	2,733
Clerical (47 hrs/yr @ $39.3563/hr)	1,866
Operator (474 hrs/yr @ $35.9445/hr)	17,043
Materials for booster pumps (calculated as a percentage of capital)	697
Materials for backwash/rinse pumps (calculated as a percentage of capital)	239
Cartridge filter replacement (58 filters/yr @ $197.9583/sf/yr)	11,402
Facility maintenance (materials and labor) (4700 sf @ $5.9929/sf/yr)	28,166
Sodium Hydroxide - Small Qty (79132 lbs/yr @ $0.302/lb)	23,895
Perchlorate-selective (479 cf/yr @ $256.5165/cf)	122,919
Energy for booster pumps (216 Mwh/yr @ $0.1212/kwh)	26,226
Energy for backwash/rinse pumps (0 Mwh/yr @ $0.1212/kwh)	0
Energy for lighting (4 Mwh/yr @ $0.1212/kwh)	540
Energy for ventilation (4 Mwh/yr @ $0.1212/kwh)	444
Heat pump (cooling mode) (39 Mwh/yr @ $0.1212/kwh)	4,732
Heat pump (62 Mwh/yr @ $0.1212/kwh)	7,516
POTW discharge fees (16757 gal/yr @ $0.1762/gal)	2,953
Spent resin disposal (10 ton/yr @ $697.6744/ton)	7,188
Spent cartridge filter disposal (1 ton/yr @ $74.9152/ton)	52
Miscellaneous Allowance (0 @ $)	25,861

Anion Exchange for Perchlorate, design 56.271 mgd, average 28.136 mgd, High-Cost Components, Resin type: Perchlorate-selective 250,000 BV

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1	Pressure Vessels - Stainless Steel	6,247,920	35
2.1	Ion Exchange Resin - Perchlorate-selective	4,672,704	N/A
3.4.1	Caustic Storage Tanks - Stainless Steel	20,040	35
3.4.2	Caustic Storage Tanks - Heat Tracing	2,341	10
3.4.3	Caustic Storage Tanks - Insulation	4,613	10
3.5.1	Caustic Day Tanks - Stainless Steel	5,461	35
3.5.2	Caustic Day Tanks - Heat Tracing	1,544	10
3.5.3	Caustic Day Tanks - Insulation	794	10
4.1	Cartridge Filters - Cartridge Filters	1,280,742	35
5.1.1	Backwash Piping - Stainless Steel	68,948	45
5.3.1	Process Piping - Stainless Steel	65,361	45
5.5.1	Inlet and Outlet Piping - Stainless Steel	127,977	45
5.7.1	Caustic Piping - Stainless Steel	27,579	45
5.8.1	Residuals Piping - Stainless Steel	29,507	45
5.8.2	Residuals Piping - Excavation	1,334	45
5.8.3	Residuals Piping - Bedding	79	45
5.8.4	Residuals Piping - Backfill and Compaction	618	45
5.8.5	Residuals Piping - Thrust Blocks	1,070	45
6.1.1	Valves and Fittings - Motor/Air Operated (on/off) - Process - Stainless Steel	1,247,412	25
6.1.2	Valves and Fittings - Motor/Air Operated (on/off) - Backwash - Stainless Steel	405,104	25
6.1.6	Valves and Fittings - Motor/Air Operated (on/off) - Caustic - Stainless Steel	8,267	25
6.2.1	Valves and Fittings - Manual - Inlet and outlet - Cast Iron	22,996	25
6.2.2	Valves and Fittings - Manual - Process - Stainless Steel	337,430	25
6.3.1	Valves and Fittings - Check Valves - Backwash - Stainless Steel	9,128	25
6.3.2	Valves and Fittings - Check Valves - Inlet and Outlet - Stainless Steel	75,474	25
6.3.7	Valves and Fittings - Check Valves - Residuals - Stainless Steel	3,068	25
7.1	Pumps - Booster	412,163	20
7.2	Pumps - Backwash/Rinse	42,669	20
8.2.1	Mixers for Caustic Storage Tanks - Mounted	3,221	25
8.3.1	Mixers for Caustic Day Tanks - Mounted	1,765	25
11.1.1	Instrumentation and Controls - Flow Meters - Inlet and Outlet - Orifice Plate	12,366	15
11.3.1	Instrumentation and Controls - Flow Meters - Backwash - Magnetic	8,824	15
11.4.1	Instrumentation and Controls - Flow Meters - Residuals - Magnetic	6,832	15
11.9	Instrumentation and Controls - High/Low Alarm (for caustic tanks)	1,185	15
11.11	Instrumentation and Controls - Temperature meters	593	15
11.12	Instrumentation and Controls - Head loss sensors	95,449	15
11.13.1	Instrumentation and Controls - Sampling Ports - Carbon Steel	1,300	25
11.17	Instrumentation and Controls - Turbidity meters	5,223	15
12.1.1	System Controls - PLC Units - PLC racks/power supplies	1,361	10
12.1.2	System Controls - PLC Units - CPUs	1,256	10
12.1.3	System Controls - PLC Units - I/O discrete input modules	1,227	10
12.1.4	System Controls - PLC Units - I/O discrete output modules	375	10
12.1.5	System Controls - PLC Units - I/O combination analog modules	14,359	10
12.1.6	System Controls - PLC Units - Ethernet modules	1,730	10
12.1.7	System Controls - PLC Units - Base expansion modules	355	10
12.1.8	System Controls - PLC Units - Base expansion controller modules	257	10
12.1.9	System Controls - PLC Units - UPSs	563	10
12.2.1	System Controls - Operator Equipment - Drive controllers	9,652	15
12.2.2	System Controls - Operator Equipment - Operator interface units	920	10
12.2.3	System Controls - Operator Equipment - PC Workstations	1,006	10
12.2.4	System Controls - Operator Equipment - Printers - laser jet	627	10
12.2.5	System Controls - Operator Equipment - Printers - dot matrix	642	10

WBS #	Item	Total Cost ($)	Useful Life (yrs)
12.3.1	System Controls - Controls Software - Operator interface software	366	10
12.3.2	System Controls - Controls Software - PLC programming software	474	10
12.3.3	System Controls - Controls Software - PLC data collection software	690	10
12.3.4	System Controls - Controls Software - Plant intelligence software	11,480	10
13.1.1	Building Structures and HVAC - Building 1 - High Quality	1,555,399	40
13.1.2.1	Building Structures and HVAC - Building 1 - Heating System - Natural gas condensing furnace	64,314	25
13.1.3.1	Building Structures and HVAC - Building 1 - Cooling System - Air conditioner	25,745	25
13.2.1	Building Structures and HVAC - Building 2 - High Quality	412,924	40
13.2.3.1	Building Structures and HVAC - Building 2 - Heating and Cooling System - Heat pump	34,649	25
13.3	Building Structures and HVAC - Concrete Pad	236,511	40
Indirect	Indirect and Add-On Costs (contingency from model)	9,150,973	40
	Process Cost	**17,635,986**	
	System Cost	**26,786,959**	
	O&M Cost	**2,713,642**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Construction Management	749,880
Process Engineering	1,410,879
Site Work	262,459
Yard Piping	195,489
Geotechnical	32,795
Standby Power	147,274
Electrical (including yard wiring)	1,530,645
Mobilization and Demobilization	431,365
Architectural Fees for Treatment Building	144,432
Permits	1,731
Pilot Study	69,717
Land Cost	91,577
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Contingency (6.2%)	1,084,613
Miscellaneous Allowance (10.0%)	1,763,599
Legal, Fiscal, and Administrative (2.0%)	352,720
Sales Tax (0.0%)	0
Financing during Construction (5.0%)	881,799

Breakdown of O&M costs	Annual Cost ($/year)
Manager (195 hrs/yr @ $71.8488/hr)	14,034
Clerical (195 hrs/yr @ $39.3563/hr)	7,688
Operator (1953 hrs/yr @ $43.8427/hr)	85,639
Materials for booster pumps (calculated as a percentage of capital)	4,122
Materials for backwash/rinse pumps (calculated as a percentage of capital)	427
Cartridge filter replacement (960 filters/yr @ $207.2477/sf/yr)	198,958
Facility maintenance (materials and labor) (20480 sf @ $5.9929/sf/yr)	122,734
Sodium Hydroxide - Large Qty (906405 lbs/yr @ $0.1254/lb)	113,672
Perchlorate-selective (5492 cf/yr @ $256.5165/cf)	1,408,734
Energy for booster pumps (2480 Mwh/yr @ $0.1212/kwh)	300,573
Energy for backwash/rinse pumps (0 Mwh/yr @ $0.1212/kwh)	3
Energy for lighting (160 Mwh/yr @ $0.1212/kwh)	19,397
Energy for ventilation (28 Mwh/yr @ $0.1212/kwh)	3,376
Air conditioning (67 Mwh/yr @ $0.1212/kwh)	8,167
Heat pump (cooling mode) (283 Mwh/yr @ $0.1212/kwh)	34,319
Heat pump (82 Mwh/yr @ $0.1212/kwh)	9,947
Natural gas condensing furnace (25251 therms/yr @ $0.7941/therm)	20,051
POTW discharge fees (189467 gal/yr @ $0.1682/gal)	31,868
Spent resin disposal (118 ton/yr @ $697.6744/ton)	82,377
Spent cartridge filter disposal (12 ton/yr @ $74.9152/ton)	863
Miscellaneous Allowance (0 @ $)	246,695

Biological Treatment, design 0.500 mgd, average 0.162 mgd, Low-Cost Components, Design Type: Fixed Bed Pressure Vessel

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1.1	Bioreactors - Pressure Vessels - Carbon Steel - Plastic Internals	61,436	30
1.3.1	Bioreactors - Media - GAC	30,950	N/A
2.1.1	Post-Treatment Filters - Filter Basins - Concrete	14,675	37
2.1.2	Post-Treatment Filters - Filter Basins - Internals (Underdrain/Backwash System)	121,148	37
2.1.3	Post-Treatment Filters - Filter Basins - Aluminum Railing	1,795	35
2.1.4	Post-Treatment Filters - Filter Basins - Aluminum Stairs	8,435	35
2.1.5	Post-Treatment Filters - Filter Basins - Excavation	8,987	37
2.1.6	Post-Treatment Filters - Filter Basins - Backfill and Compaction	3,334	37
2.3.1	Post-Treatment Filters - Media - Anthracite	7,920	8.5
2.3.2	Post-Treatment Filters - Media - Sand	3,608	20
3.2.1	Tanks - Electron Donor Storage Tanks - Plastic/XLPE	1,171	7
3.5.1	Tanks - Electron Donor Day Tanks - Plastic/XLPE	911	7
3.8.1	Tanks - Residuals Holding Tanks/Basins - Plastic/XLPE Tanks	12,401	20
3.11.1	Tanks - Aeration Tanks - Plastic/XLPE	1,596	20
3.11.2	Tanks - Aeration Tanks - Diffusers	53	10
3.12.1	Tanks - Polymer Storage Tanks - Plastic/XLPE	1,045	7
3.13.1	Tanks - Coagulant Mix Tank - Plastic/XLPE Tanks	1,571	20
4.1.1	Piping - Backwash Piping - PVC	1,134	17
4.2.1	Piping - Electron Donor Piping - PVC	101	17
4.4.1	Piping - Phosphoric Acid Piping - PVC	101	17
4.5.1	Piping - Process Piping - PVC	408	17
4.7.1	Piping - Inlet and Outlet Piping - PVC	622	17
4.8.1	Piping - Residuals Piping - PVC	219	17
4.11.1	Piping - Polymer Addition Piping - PVC	101	17
5.1.1	Valves and Fittings - Motor/Air Operated (on/off) - Process - Polypropylene/PVC	10,434	20
5.1.2	Valves and Fittings - Motor/Air Operated (on/off) - Backwash - Polypropylene/PVC	21,987	20
5.1.3	Valves and Fittings - Motor/Air Operated (on/off) - Electron Donor - Polypropylene/PVC	3,470	20
5.1.5	Valves and Fittings - Motor/Air Operated (on/off) - Phosphoric Acid - Polypropylene/PVC	2,974	20
5.1.7	Valves and Fittings - Motor/Air Operated (on/off) - Residuals - Polypropylene/PVC	1,654	20
5.1.8	Valves and Fittings - Motor/Air Operated (on/off) - Air Scour- Polypropylene/PVC	2,087	20
5.1.12	Valves and Fittings - Motor/Air Operated (on/off) - Aeration- Polypropylene/PVC	2,531	20
5.1.13	Valves and Fittings - Motor/Air Operated (on/off) - Polymer- Polypropylene/PVC	2,478	20
5.2.1	Valves and Fittings - Manual - Inlet and outlet - Polypropylene/PVC	1,282	20
5.2.2	Valves and Fittings - Manual - Process - Polypropylene/PVC	905	20
5.3.1	Valves and Fittings - Check Valves - Backwash - Polypropylene/PVC	2,262	20
5.3.2	Valves and Fittings - Check Valves - Residuals - Polypropylene/PVC	227	20
5.3.3	Valves and Fittings - Check Valves - Inlet and outlet - Polypropylene/PVC	1,353	20
5.3.5	Valves and Fittings - Check Valves - Electron Donor - Polypropylene/PVC	283	20
5.3.7	Valves and Fittings - Check Valves - Phosphoric Acid - Polypropylene/PVC	424	20
5.3.8	Valves and Fittings - Check Valves - Polymer - Polypropylene/PVC	141	20
6.4	Pumps and Blowers - Residuals Pump	13,958	17
6.5.1	Pumps and Blowers - Electron Donor Metering - PVC - Electric	1,850	15
6.7.1	Pumps and Blowers - Phosphoric Acid Metering - PVC - Electric	777	15
6.8.1	Pumps and Blowers - Blowers - Air Scour - Positive Displacement	23,134	20

WBS #	Item	Total Cost ($)	Useful Life (yrs)
6.8.3	Pumps and Blowers - Blowers - Aeration - Positive Displacement	20,390	20
6.10.1	Pumps and Blowers - Polymer Metering - PVC - Electric	5,165	15
7.1.1	Mixers - Mixers for Electron Donor Storage Tanks - Mounted	1,720	22
7.2.1	Mixers - Mixers for Electron Donor Day Tanks - Mounted	1,669	22
7.5.1	Mixers - Mixers for Phosphoric Acid Storage Tanks - Mounted	1,650	22
7.11.1	Mixers - Mixers for Polymer Storage Tanks - Mounted	1,695	22
7.12.1	Mixers - Coagulant Mix Tank Mixers - Mounted	1,752	22
8.1	Solids Transfer - Eductors for Holding Tanks	1,690	40
8.2.1	Solids Transfer - Dry Feeders for Filter Coagulant Addition - Volumetric Feeder	15,177	20
9.1.1	Instrumentation - Flow Meters - Inlet and Outlet - Propeller	4,141	14
9.3.1	Instrumentation - Flow Meters - Backwash - Propeller	4,544	14
9.4.1	Instrumentation - Flow Meters - Residuals - Propeller	1,786	14
9.7	Instrumentation - High/Low Alarm (for holding tanks)	593	14
9.8	Instrumentation - Temperature meters	2,373	14
9.9	Instrumentation - Head loss sensors	4,242	14
9.10.1	Instrumentation - Sampling Ports - Stainless Steel	350	30
9.12	Instrumentation - ORP sensor	5,265	14
9.14	Instrumentation - Turbidity meters	20,893	14
9.15	Instrumentation - Perchlorate/Nitrate Analyzer	24,574	14
9.17	Instrumentation - Dissolved Oxygen Analyzer	2,941	14
10.1.1	System Controls - PLC Unit(s) - PLC racks/power supplies	680	8
10.1.2	System Controls - PLC Unit(s) - CPUs	1,256	8
10.1.3	System Controls - PLC Unit(s) - I/O discrete input modules	614	8
10.1.4	System Controls - PLC Unit(s) - I/O discrete output modules	375	8
10.1.5	System Controls - PLC Unit(s) - I/O combination analog modules	5,874	8
10.1.6	System Controls - PLC Unit(s) - Ethernet modules	1,730	8
10.1.7	System Controls - PLC Unit(s) - Base expansion modules	118	8
10.1.8	System Controls - PLC Unit(s) - Base expansion controller modules	86	8
10.1.9	System Controls - PLC Unit(s) - UPSs	563	8
10.2.1	System Controls - Operator Equipment - Drive controllers	15,014	14
10.2.2	System Controls - Operator Equipment - Operator interface units	3,911	8
11.1.1	Building Structures and HVAC - Building 1 - Low Quality	86,721	37
11.3	Building Structures and HVAC - Concrete Pad	9,072	37
14.1	Solids drying pad	1,296	37
Indirect	Indirect and Add-On Costs (contingency from model)	425,303	37
	Process Cost	**627,852**	
	System Cost	**1,053,155**	
	O&M Cost	**52,275**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Mobilization and Demobilization	0
Architectural Fees for Treatment Building	0
Site Work	15,507
Yard Piping	3,375
Geotechnical	4,736
Standby Power	0
Electrical (including yard wiring)	53,206
Contingency	0
Process Engineering	125,570
Construction Management and GC Overhead	11,913
Permits	903
Pilot Study	132,669
Land Cost	2,082
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	62,785
Legal, Fiscal, and Administrative (2.0%)	12,557
Sales Tax (0.0%)	0
Financing during Construction (0.0%)	0

Breakdown of O&M costs	Annual Cost ($/year)
Manager (45 hrs/yr @ $45.2396/hr)	2,049
Administrative (45 hrs/yr @ $31.9149/hr)	1,446
Operator (321 hrs/yr @ $30.4776/hr)	9,776
Materials for residuals pumps (calculated as a percentage of capital)	140
Materials for backwash air scour blowers (calculated as a percentage of capital)	231
Materials for aeration blowers (calculated as a percentage of capital)	204
Materials for filter basins (calculated as a percentage of capital)	1,404
Facility maintenance (materials and labor) (1100 sf @ $5.7866/sf/yr)	6,365
Acetic Acid (24657 lbs/yr @ $0.0978/lb)	2,412
Phosphoric Acid - Small Qty (2086 lbs/yr @ $0.5492/lb)	1,145
Ferric Chloride - Small Qty (4931 lbs/yr @ $0.9961/lb)	4,912
Polymers - Large Qty (2521 lbs/yr @ $0.8113/lb)	2,045
GAC annual attrition replacement - Bioreactor (1701 lbs/yr @ $1.9176/lb)	3,262
Sand annual attrition replacement- Filter (15 cuft/yr @ $23.5561/cuft)	361
Anthracite annual attrition replacement- Filter (1555 lbs/yr @ $0.5093/lb)	792
Consumables for online perchlorate analysis (NA)	10,117
Energy for backwash pumps (2 Mwh/yr @ $0.1212/kwh)	230
Energy for residuals pumps (0 Mwh/yr @ $0.1212/kwh)	15
Energy for blowers (1 Mwh/yr @ $0.1212/kwh)	100
Energy for lighting (0 Mwh/yr @ $0.1212/kwh)	60
Energy for ventilation (1 Mwh/yr @ $0.1212/kwh)	74
Holding basins solids disposal (5 ton/yr @ $74.9152/ton)	381
Miscellaneous Allowance (0 @ $)	4,752

Biological Treatment, design 5.809 mgd, average 2.455 mgd, Mid-Cost Components, Design Type: Fixed Bed Gravity Basin

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.2.1	Bioreactors - Gravity Basins - Concrete	106,224	40
1.2.2	Bioreactors - Gravity Basins - Internals (Underdrain/Backwash System)	492,141	40
1.2.3	Bioreactors - Gravity Basins - Aluminum Railing	8,526	40
1.2.4	Bioreactors - Gravity Basins - Aluminum Stairs	8,435	40
1.2.5	Bioreactors - Gravity Basins - Excavation	48,763	40
1.2.6	Bioreactors - Gravity Basins - Backfill and Compaction	11,850	40
1.3.1	Bioreactors - Media - GAC	406,254	N/A
2.1.1	Post-Treatment Filters - Filter Basins - Concrete	96,486	40
2.1.2	Post-Treatment Filters - Filter Basins - Internals (Underdrain/Backwash System)	413,581	40
2.1.3	Post-Treatment Filters - Filter Basins - Aluminum Railing	7,068	40
2.1.4	Post-Treatment Filters - Filter Basins - Aluminum Stairs	8,435	40
2.1.5	Post-Treatment Filters - Filter Basins - Excavation	41,825	40
2.1.6	Post-Treatment Filters - Filter Basins - Backfill and Compaction	10,826	40
2.3.1	Post-Treatment Filters - Media - Anthracite	110,417	10
2.3.2	Post-Treatment Filters - Media - Sand	50,308	20
3.1.1	Tanks - Backwash Tanks - Fiberglass	57,627	25
3.2.1	Tanks - Electron Donor Storage Tanks - Fiberglass	10,837	10
3.4.1	Tanks - Phosphoric Acid Storage Tanks - Fiberglass	4,705	10
3.5.1	Tanks - Electron Donor Day Tanks - Fiberglass	5,874	10
3.7.1	Tanks - Phosphoric Acid Day Tanks - Fiberglass	4,705	10
3.8.1	Tanks - Residuals Holding Tanks/Basins - Concrete Basins (includes Excavation, Backfill, and Compaction)	150,286	40
3.11.1	Tanks - Aeration Tanks - Fiberglass	12,202	25
3.11.2	Tanks - Aeration Tanks - Diffusers	413	10
3.12.1	Tanks - Polymer Storage Tanks - Fiberglass	9,932	10
3.13.1	Tanks - Coagulant Mix Tank - Fiberglass Tanks	11,769	25
4.1.1	Piping - Backwash Piping - CPVC	32,516	22
4.2.1	Piping - Electron Donor Piping - CPVC	352	22
4.4.1	Piping - Phosphoric Acid Piping - CPVC	352	22
4.5.1	Piping - Process Piping - CPVC	17,733	22
4.7.1	Piping - Inlet and Outlet Piping - CPVC	36,114	22
4.8.1	Piping - Residuals Piping - CPVC	4,003	22
4.11.1	Piping - Polymer Addition Piping - CPVC	480	22
5.1.1	Valves and Fittings - Motor/Air Operated (on/off) - Process - Cast Iron	231,488	25
5.1.2	Valves and Fittings - Motor/Air Operated (on/off) - Backwash - Cast Iron	114,008	25
5.1.3	Valves and Fittings - Motor/Air Operated (on/off) - Electron Donor - Stainless Steel	4,163	25
5.1.5	Valves and Fittings - Motor/Air Operated (on/off) - Phosphoric Acid - Stainless Steel	4,163	25
5.1.7	Valves and Fittings - Motor/Air Operated (on/off) - Residuals - Cast Iron	5,311	25
5.1.8	Valves and Fittings - Motor/Air Operated (on/off) - Air Scour- Cast Iron	6,822	25
5.1.12	Valves and Fittings - Motor/Air Operated (on/off) - Aeration- Cast Iron	7,440	25
5.1.13	Valves and Fittings - Motor/Air Operated (on/off) - Polymer-Polypropylene/PVC	2,614	25
5.2.1	Valves and Fittings - Manual - Inlet and outlet - Cast Iron	5,215	25
5.3.1	Valves and Fittings - Check Valves - Backwash - Cast Iron	7,911	25
5.3.2	Valves and Fittings - Check Valves - Residuals - Cast Iron	2,164	25
5.3.3	Valves and Fittings - Check Valves - Inlet and outlet - Cast Iron	5,234	25
5.3.5	Valves and Fittings - Check Valves - Electron Donor - Stainless Steel	1,032	25
5.3.7	Valves and Fittings - Check Valves - Phosphoric Acid - Stainless Steel	1,547	25
5.3.8	Valves and Fittings - Check Valves - Polymer - Polypropylene/PVC	180	25
6.1	Pumps and Blowers - Booster Pump	69,732	20

WBS #	Item	Total Cost ($)	Useful Life (yrs)
6.3	Pumps and Blowers - Backwash Pump	83,511	20
6.4	Pumps and Blowers - Residuals Pump	20,314	20
6.5.1	Pumps and Blowers - Electron Donor Metering - Stainless Steel - Electric	5,993	20
6.7.1	Pumps and Blowers - Phosphoric Acid Metering - PVC - Electric	1,612	20
6.8.1	Pumps and Blowers - Blowers - Air Scour - Positive Displacement	58,928	25
6.8.3	Pumps and Blowers - Blowers - Aeration - Positive Displacement	34,152	25
6.10.1	Pumps and Blowers - Polymer Metering - Stainless Steel - Motor Driven	14,614	20
7.1.1	Mixers - Mixers for Electron Donor Storage Tanks - Mounted	2,681	25
7.2.1	Mixers - Mixers for Electron Donor Day Tanks - Mounted	1,853	25
7.5.1	Mixers - Mixers for Phosphoric Acid Storage Tanks - Mounted	1,706	25
7.6.1	Mixers - Mixers for Phosphoric Acid Day Tanks - Mounted	1,651	25
7.11.1	Mixers - Mixers for Polymer Storage Tanks - Mounted	2,534	25
7.12.1	Mixers - Coagulant Mix Tank Mixers - Mounted	2,781	25
8.1	Solids Transfer - Eductors for Holding Tanks	9,084	45
8.2.1	Solids Transfer - Dry Feeders for Filter Coagulant Addition - Volumetric Feeder	15,180	25
9.1.1	Instrumentation - Flow Meters - Inlet and Outlet - Venturi	17,176	15
9.3.1	Instrumentation - Flow Meters - Backwash - Venturi	15,837	15
9.4.1	Instrumentation - Flow Meters - Residuals - Venturi	9,686	15
9.5	Instrumentation - Level Switch/Alarm (for vessels)	2,963	15
9.6	Instrumentation - High/Low Alarm (for backwash tanks)	593	15
9.7	Instrumentation - High/Low Alarm (for holding tanks)	593	15
9.8	Instrumentation - Temperature meters	5,933	15
9.9	Instrumentation - Head loss sensors	10,605	15
9.10.1	Instrumentation - Sampling Ports - Carbon Steel	700	25
9.12	Instrumentation - ORP sensor	5,265	15
9.14	Instrumentation - Turbidity meters	57,455	15
9.15	Instrumentation - Perchlorate/Nitrate Analyzer	24,574	15
9.17	Instrumentation - Dissolved Oxygen Analyzer	2,941	15
10.1.1	System Controls - PLC Unit(s) - PLC racks/power supplies	1,361	10
10.1.2	System Controls - PLC Unit(s) - CPUs	1,256	10
10.1.3	System Controls - PLC Unit(s) - I/O discrete input modules	921	10
10.1.4	System Controls - PLC Unit(s) - I/O discrete output modules	375	10
10.1.5	System Controls - PLC Unit(s) - I/O combination analog modules	11,748	10
10.1.6	System Controls - PLC Unit(s) - Ethernet modules	1,730	10
10.1.7	System Controls - PLC Unit(s) - Base expansion modules	355	10
10.1.8	System Controls - PLC Unit(s) - Base expansion controller modules	257	10
10.1.9	System Controls - PLC Unit(s) - UPSs	563	10
10.2.1	System Controls - Operator Equipment - Drive controllers	20,376	15
10.2.2	System Controls - Operator Equipment - Operator interface units	920	10
10.2.3	System Controls - Operator Equipment - PC Workstations	1,006	10
10.2.4	System Controls - Operator Equipment - Printers - laser jet	627	10
10.2.5	System Controls - Operator Equipment - Printers - dot matrix	642	10
10.3.1	System Controls - Controls Software - Operator interface software	366	10
10.3.2	System Controls - Controls Software - PLC programming software	474	10
10.3.3	System Controls - Controls Software - PLC data collection software	690	10
10.3.4	System Controls - Controls Software - Plant intelligence software	11,480	10
11.1.1	Building Structures and HVAC - Building 1 - Medium Quality	479,622	40
11.1.3.1	Building Structures and HVAC - Building 1 - Heating and Cooling System - Heat pump	3,812	25
11.2.1	Building Structures and HVAC - Building 2 - Medium Quality	748,150	40
11.2.3.1	Building Structures and HVAC - Building 2 - Heating and Cooling System - Heat pump	13,213	25
11.3	Building Structures and HVAC - Concrete Pad	183,377	40
14.1	Solids drying pad	7,128	40

WBS #	Item	Total Cost ($)	Useful Life (yrs)
Indirect	Indirect and Add-On Costs (contingency from model)	2,835,055	40
	Process Cost	**4,551,427**	
	System Cost	**7,386,482**	
	O&M Cost	**511,935**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Mobilization and Demobilization	226,694
Architectural Fees for Treatment Building	88,547
Site Work	206,712
Yard Piping	51,461
Geotechnical	62,238
Standby Power	28,054
Electrical (including yard wiring)	312,325
Contingency	0
Process Engineering	546,171
Construction Management and GC Overhead	286,932
Permits	7,622
Pilot Study	212,082
Land Cost	32,474
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	455,143
Legal, Fiscal, and Administrative (2.0%)	91,029
Sales Tax (0.0%)	0
Financing during Construction (5.0%)	227,571

Breakdown of O&M costs	Annual Cost ($/year)
Manager (199 hrs/yr @ $57.6375/hr)	11,493
Administrative (199 hrs/yr @ $35.9445/hr)	7,167
Operator (1365 hrs/yr @ $39.3563/hr)	53,734
Materials for booster pumps (calculated as a percentage of capital)	697
Materials for backwash pumps (calculated as a percentage of capital)	835
Materials for residuals pumps (calculated as a percentage of capital)	203
Materials for backwash air scour blowers (calculated as a percentage of capital)	589
Materials for aeration blowers (calculated as a percentage of capital)	342
Materials forbioreactor basins (calculated as a percentage of capital)	6,153
Materials for filter basins (calculated as a percentage of capital)	4,709
Facility maintenance (materials and labor) (15560 sf @ $5.9929/sf/yr)	93,249
Acetic Acid (373663 lbs/yr @ $0.0978/lb)	36,551
Phosphoric Acid - Small Qty (31607 lbs/yr @ $0.5492/lb)	17,359
Ferric Chloride - Small Qty (74733 lbs/yr @ $0.9961/lb)	74,442
Polymers - Large Qty (48210 lbs/yr @ $0.8113/lb)	39,113
GAC annual attrition replacement - Bioreactor (19440 lbs/yr @ $1.8038/lb)	35,065
Sand annual attrition replacement- Filter (178 cuft/yr @ $23.5561/cuft)	4,192
Anthracite annual attrition replacement- Filter (18067 lbs/yr @ $0.5093/lb)	9,201
Consumables for online perchlorate analysis (NA)	10,117
Energy for booster pumps (216 Mwh/yr @ $0.1212/kwh)	26,226
Energy for backwash pumps (14 Mwh/yr @ $0.1212/kwh)	1,754
Energy for residuals pumps (9 Mwh/yr @ $0.1212/kwh)	1,108
Energy for blowers (10 Mwh/yr @ $0.1212/kwh)	1,188
Energy for lighting (62 Mwh/yr @ $0.1212/kwh)	7,522
Energy for ventilation (6 Mwh/yr @ $0.1212/kwh)	698
Heat pump (cooling mode) (54 Mwh/yr @ $0.1212/kwh)	6,509
Heat pump (99 Mwh/yr @ $0.1212/kwh)	12,003
Holding basins solids disposal (42 ton/yr @ $74.9152/ton)	3,175
Miscellaneous Allowance (0 @ $)	46,540

Biological Treatment, design 56.271 mgd, average 28.136 mgd, High-Cost Components, Design Type: Fluidized Bed Pressure Vessel

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1.1	Bioreactors - Pressure Vessels - Stainless Steel	16,981,071	35
1.3.1	Bioreactors - Media - GAC	2,776,373	N/A
2.1.1	Post-Treatment Filters - Filter Basins - Concrete	509,517	40
2.1.2	Post-Treatment Filters - Filter Basins - Internals (Underdrain/Backwash System)	1,692,172	40
2.1.3	Post-Treatment Filters - Filter Basins - Aluminum Railing	25,802	40
2.1.4	Post-Treatment Filters - Filter Basins - Aluminum Stairs	8,435	40
2.1.5	Post-Treatment Filters - Filter Basins - Excavation	236,337	40
2.1.6	Post-Treatment Filters - Filter Basins - Backfill and Compaction	41,320	40
2.3.1	Post-Treatment Filters - Media - Anthracite	1,039,884	10
2.3.2	Post-Treatment Filters - Media - Sand	473,789	20
3.2.1	Tanks - Electron Donor Storage Tanks - Stainless Steel	115,623	35
3.4.1	Tanks - Phosphoric Acid Storage Tanks - Fiberglass	4,944	10
3.5.1	Tanks - Electron Donor Day Tanks - Stainless Steel	19,303	35
3.7.1	Tanks - Phosphoric Acid Day Tanks - Fiberglass	4,944	10
3.8.1	Tanks - Residuals Holding Tanks/Basins - Steel Tanks	139,334	35
3.11.1	Tanks - Aeration Tanks - Steel	87,651	35
3.11.2	Tanks - Aeration Tanks - Diffusers	3,636	10
3.12.1	Tanks - Polymer Storage Tanks - Stainless Steel	25,447	35
3.13.1	Tanks - Coagulant Mix Tank - Steel Tanks	84,632	35
4.1.1	Piping - Backwash Piping - Stainless Steel	141,470	45
4.2.1	Piping - Electron Donor Piping - Stainless Steel	3,657	45
4.4.1	Piping - Phosphoric Acid Piping - Stainless Steel	3,657	45
4.5.1	Piping - Process Piping - Stainless Steel	88,253	45
4.7.1	Piping - Inlet and Outlet Piping - Stainless Steel	204,762	45
4.8.1	Piping - Residuals Piping - Stainless Steel	9,102	45
4.9.1	Piping - Fluidized Bed Recycle Piping - Stainless Steel	70,544	45
4.11.1	Piping - Polymer Addition Piping - Stainless Steel	7,801	45
5.1.1	Valves and Fittings - Motor/Air Operated (on/off) - Process - Stainless Steel	1,355,857	25
5.1.2	Valves and Fittings - Motor/Air Operated (on/off) - Backwash - Stainless Steel	785,358	25
5.1.3	Valves and Fittings - Motor/Air Operated (on/off) - Electron Donor - Stainless Steel	27,895	25
5.1.5	Valves and Fittings - Motor/Air Operated (on/off) - Phosphoric Acid - Stainless Steel	27,895	25
5.1.7	Valves and Fittings - Motor/Air Operated (on/off) - Residuals - Stainless Steel	2,012	25
5.1.8	Valves and Fittings - Motor/Air Operated (on/off) - Air Scour- Stainless Steel	16,535	25
5.1.9	Valves and Fittings - Motor/Air Operated (on/off) - Fluidized Bed Recycle - Stainless Steel	269,670	25
5.1.11	Valves and Fittings - Motor/Air Operated (on/off) - Air Biomass Removal- Stainless Steel	6,007	25
5.1.12	Valves and Fittings - Motor/Air Operated (on/off) - Aeration- Stainless Steel	70,204	25
5.1.13	Valves and Fittings - Motor/Air Operated (on/off) - Polymer- Stainless Steel	3,353	25
5.2.1	Valves and Fittings - Manual - Inlet and outlet - Cast Iron	22,996	25
5.2.2	Valves and Fittings - Manual - Process - Stainless Steel	459,469	25
5.3.1	Valves and Fittings - Check Valves - Backwash - Stainless Steel	26,164	25
5.3.2	Valves and Fittings - Check Valves - Residuals - Stainless Steel	868	25
5.3.3	Valves and Fittings - Check Valves - Inlet and outlet - Stainless Steel	37,737	25
5.3.5	Valves and Fittings - Check Valves - Electron Donor - Stainless Steel	1,032	25
5.3.7	Valves and Fittings - Check Valves - Phosphoric Acid - Stainless Steel	1,547	25
5.3.8	Valves and Fittings - Check Valves - Polymer - Stainless Steel	868	25

WBS #	Item	Total Cost ($)	Useful Life (yrs)
6.1	Pumps and Blowers - Booster Pump	412,163	20
6.2	Pumps and Blowers - Recycle Pump	302,373	20
6.3	Pumps and Blowers - Backwash Pump	158,883	20
6.4	Pumps and Blowers - Residuals Pump	30,540	20
6.5.1	Pumps and Blowers - Electron Donor Metering - Stainless Steel - Motor Driven	11,689	20
6.7.1	Pumps and Blowers - Phosphoric Acid Metering - PVC - Motor Driven	5,938	20
6.8.1	Pumps and Blowers - Blowers - Air Scour - Positive Displacement	59,261	25
6.8.2	Pumps and Blowers - Blowers - Biomass Removal - Positive Displacement	15,178	25
6.8.3	Pumps and Blowers - Blowers - Aeration - Positive Displacement	143,920	25
6.10.1	Pumps and Blowers - Polymer Metering - Stainless Steel - Motor Driven	15,347	20
7.1.1	Mixers - Mixers for Electron Donor Storage Tanks - Impeller	24,687	25
7.2.1	Mixers - Mixers for Electron Donor Day Tanks - Mounted	3,156	25
7.5.1	Mixers - Mixers for Phosphoric Acid Storage Tanks - Mounted	2,309	25
7.6.1	Mixers - Mixers for Phosphoric Acid Day Tanks - Mounted	1,692	25
7.11.1	Mixers - Mixers for Polymer Storage Tanks - Mounted	3,668	25
7.12.1	Mixers - Coagulant Mix Tank Mixers - Impeller	18,263	25
8.1	Solids Transfer - Eductors for Holding Tanks	15,000	45
8.2.1	Solids Transfer - Dry Feeders for Filter Coagulant Addition - Volumetric Feeder	15,205	25
9.1.1	Instrumentation - Flow Meters - Inlet and Outlet - Orifice Plate	12,366	15
9.3.1	Instrumentation - Flow Meters - Backwash - Magnetic	21,398	15
9.4.1	Instrumentation - Flow Meters - Residuals - Magnetic	3,868	15
9.7	Instrumentation - High/Low Alarm (for holding tanks)	593	15
9.8	Instrumentation - Temperature meters	73,569	15
9.9	Instrumentation - Head loss sensors	131,508	15
9.10.1	Instrumentation - Sampling Ports - Carbon Steel	3,950	25
9.12	Instrumentation - ORP sensor	5,265	15
9.14	Instrumentation - Turbidity meters	396,960	15
9.15	Instrumentation - Perchlorate/Nitrate Analyzer	24,574	15
9.17	Instrumentation - Dissolved Oxygen Analyzer	2,941	15
10.1.1	System Controls - PLC Unit(s) - PLC racks/power supplies	4,082	10
10.1.2	System Controls - PLC Unit(s) - CPUs	1,256	10
10.1.3	System Controls - PLC Unit(s) - I/O discrete input modules	2,455	10
10.1.4	System Controls - PLC Unit(s) - I/O discrete output modules	750	10
10.1.5	System Controls - PLC Unit(s) - I/O combination analog modules	49,604	10
10.1.6	System Controls - PLC Unit(s) - Ethernet modules	1,730	10
10.1.7	System Controls - PLC Unit(s) - Base expansion modules	1,302	10
10.1.8	System Controls - PLC Unit(s) - Base expansion controller modules	942	10
10.1.9	System Controls - PLC Unit(s) - UPSs	563	10
10.2.1	System Controls - Operator Equipment - Drive controllers	30,028	15
10.2.2	System Controls - Operator Equipment - Operator interface units	920	10
10.2.3	System Controls - Operator Equipment - PC Workstations	1,006	10
10.2.4	System Controls - Operator Equipment - Printers - laser jet	627	10
10.2.5	System Controls - Operator Equipment - Printers - dot matrix	642	10
10.3.1	System Controls - Controls Software - Operator interface software	366	10
10.3.2	System Controls - Controls Software - PLC programming software	474	10
10.3.3	System Controls - Controls Software - PLC data collection software	690	10
10.3.4	System Controls - Controls Software - Plant intelligence software	11,480	10
11.1.1	Building Structures and HVAC - Building 1 - High Quality	3,785,520	40
11.1.2.1	Building Structures and HVAC - Building 1 - Heating System - Natural gas condensing furnace	186,719	25
11.1.3.1	Building Structures and HVAC - Building 1 - Cooling System - Air conditioner	127,120	25
11.2.1	Building Structures and HVAC - Building 2 - High Quality	927,051	40

WBS #	Item	Total Cost ($)	Useful Life (yrs)
11.2.2.1	Building Structures and HVAC - Building 2 - Heating System - Natural gas condensing furnace	97,694	25
11.2.3.1	Building Structures and HVAC - Building 2 - Cooling System - Air conditioner	280,408	25
11.3	Building Structures and HVAC - Concrete Pad	664,821	40
14.1	Solids drying pad	9,720	40
Indirect	Indirect and Add-On Costs (contingency from model)	19,972,073	40
	Process Cost	**36,019,163**	
	System Cost	**55,991,236**	
	O&M Cost	**3,636,058**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Mobilization and Demobilization	880,869
Architectural Fees for Treatment Building	321,675
Site Work	730,092
Yard Piping	255,323
Geotechnical	203,370
Standby Power	238,619
Electrical (including yard wiring)	2,994,983
Contingency	3,243,958
Process Engineering	2,881,533
Construction Management and GC Overhead	1,510,943
Permits	32,593
Pilot Study	347,913
Land Cost	206,944
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	3,601,916
Legal, Fiscal, and Administrative (2.0%)	720,383
Sales Tax (0.0%)	0
Financing during Construction (5.0%)	1,800,958

Breakdown of O&M costs	Annual Cost ($/year)
Manager (540 hrs/yr @ $71.8488/hr)	38,763
Administrative (540 hrs/yr @ $43.8427/hr)	23,653
Operator (4578 hrs/yr @ $39.3563/hr)	180,188
Materials for booster pumps (calculated as a percentage of capital)	4,122
Materials for backwash pumps (calculated as a percentage of capital)	1,589
Materials for recycle pumps (calculated as a percentage of capital)	3,024
Materials for residuals pumps (calculated as a percentage of capital)	305
Materials for backwash air scour blowers (calculated as a percentage of capital)	744
Materials for aeration blowers (calculated as a percentage of capital)	1,439
Materials for filter basins (calculated as a percentage of capital)	19,627
Facility maintenance (materials and labor) (56180 sf @ $5.9929/sf/yr)	336,679
Acetic Acid (4282440 lbs/yr @ $0.0978/lb)	418,894
Phosphoric Acid - Small Qty (362238 lbs/yr @ $0.5492/lb)	198,943
Ferric Chloride - Small Qty (856488 lbs/yr @ $0.9961/lb)	853,160
Polymers - Large Qty (123761 lbs/yr @ $0.8113/lb)	100,407
GAC annual attrition replacement - Bioreactor (83034 lbs/yr @ $1.6718/lb)	138,819
Sand annual attrition replacement- Filter (1724 cuft/yr @ $23.5561/cuft)	40,610
Anthracite annual attrition replacement- Filter (175011 lbs/yr @ $0.5093/lb)	89,133
Consumables for online perchlorate analysis (NA)	10,117
Energy for booster pumps (2480 Mwh/yr @ $0.1212/kwh)	300,573
Energy for recycle pumps (1240 Mwh/yr @ $0.1212/kwh)	150,286
Energy for backwash pumps (36 Mwh/yr @ $0.1212/kwh)	4,343
Energy for blowers (150 Mwh/yr @ $0.1212/kwh)	18,183
Energy for lighting (1212 Mwh/yr @ $0.1212/kwh)	146,962
Energy for ventilation (117 Mwh/yr @ $0.1212/kwh)	14,167
Air conditioning (685 Mwh/yr @ $0.1212/kwh)	82,991
Natural gas condensing furnace (142420 therms/yr @ $0.7941/therm)	113,090
Holding basins solids disposal (196 ton/yr @ $74.9152/ton)	14,695
Miscellaneous Allowance (0 @ $)	330,551

Reverse Osmosis / Nanofiltration, design 0.500 mgd, average 0.162 mgd, Low-Cost Components, Feed Water: High Qual GW

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1	Membrane Process - Membrane Elements	42,359	N/A
1.2	Membrane Process - RO Pressure Vessels	15,339	17
1.3.1	Membrane Process - Feed Line Connectors - Victaulic, Painted	1,341	20
1.5.1	Membrane Process - Piping On Rack - Feed - Stainless Steel	7,454	40
1.5.2	Membrane Process - Piping On Rack - Permeate - PVC	245	40
1.5.3	Membrane Process - Piping On Rack - Concentrate - Stainless Steel	5,573	40
1.6	Membrane Process - Vessel Support Rack - Steel Beams	13,663	20
1.7	Membrane Process - Markup for Rack Assembly	30,343	22
2.1.1	Pretreatment Acid Tanks - Plastic (HXLPE)	1,015	7
2.2.1	Pretreatment Antiscalant Tanks - Plastic (XLPE)	823	7
2.3.1	Cleaning Solution Makeup Tanks - Plastic (XLPE)	2,274	7
2.4.1	Cleaning Chemical Storage Tanks - Acid storage - Plastic (XLPE)	799	7
2.4.2	Cleaning Chemical Storage Tanks - High pH storage - Plastic (XLPE)	799	7
2.8.1	Acid Day Tanks - Plastic/XLPE	814	7
2.10.1	Mixers for Antiscalant Storage Tanks - Mounted	1,652	22
3.1.1	Inlet and Outlet Piping - PVC	622	17
3.2.1	Cleaning System Piping - PVC	204	17
3.3.1	Residuals Piping - PVC	612	17
3.3.2	Residuals Piping - Excavation	1,187	17
3.3.3	Residuals Piping - Bedding	70	17
3.3.4	Residuals Piping - Backfill and Compaction	550	17
3.3.5	Residuals Piping - Thrust Blocks	409	17
4.1.1	Motor/Air Operated (on/off) Valves - Pretreatment acid - Polypropylene/PVC	1,983	20
4.1.2	Motor/Air Operated (on/off) Valves - Antiscalant - Polypropylene/PVC	1,983	20
4.1.3	Motor/Air Operated (on/off) Valves - Feed line - Polypropylene/PVC	4,174	20
4.1.4	Motor/Air Operated (on/off) Valves - Concentrate control - Cast Iron	2,770	20
4.1.10	Motor/Air Operated (on/off) Valves - Cleaning - Polypropylene/PVC	25,042	20
4.2.1	Manual Valves - Inlet and outlet - Polypropylene/PVC	1,282	20
4.3.1	Check Valves - Residuals - Polypropylene/PVC	680	20
4.3.2	Check Valves - Inlet - Polypropylene/PVC	1,353	20
4.3.4	Check Valves - Feed pumps - Polypropylene/PVC	1,360	20
4.3.5	Check Valves - Cleaning - Polypropylene/PVC	2,040	20
5.1.1	Acid Metering Pumps for Pretreatment - PVC - Electric	1,582	15
5.2.1	Antiscalant Metering Pumps for Pretreatment - PVC - Electric	887	15
5.4	Pumps - Feed Water	34,730	17
5.7	Pumps - Cleaning Pumps (separate for acid and caustic)	2,901	17
6.1	Screens and Filters - Cartridge Filters for Feed	32,089	30
6.2.1	Screens and Filters - Security Screens for Cleaning - Simplex Basket Screens	11,080	30
6.3	Screens and Filters - Cartridge Filters for Cleaning	16,481	30
8.1	Teflon Immersion Heaters for Cleaning Tanks	3,321	14
9.1.1	Instrumentation - Flow Meters - Inlet and Outlet - Propeller	8,283	14
9.2.1	Instrumentation - Flow Meters - Membrane Trains - Feed Line - Propeller	7,289	14
9.3.1	Instrumentation - Flow Meters - Membrane Trains - Permeate Line - Propeller	7,289	14
9.3.1	Instrumentation - Flow Meters - Membrane Trains - Concentrate Line - Propeller	5,905	14
9.4.1	Instrumentation - Flow Meters - Cleaning - Propeller	12,424	14
9.5.1	Instrumentation - Propeller	3,645	14
9.6	Instrumentation - Level Switches/Alarms (for cleaning tanks)	1,185	14
9.7	Instrumentation - High/Low Alarms (for pretreatment chemical tanks)	1,185	14
9.8	Instrumentation - High/Low Alarms (for cleaning chemical storage tanks)	1,185	14
9.1	Instrumentation - pH meters	10,530	14

WBS #	Item	Total Cost ($)	Useful Life (yrs)
9.11	Instrumentation - Temperature meters	1,780	14
9.12	Instrumentation - Conductivity meters	12,927	14
9.13	Instrumentation - Head loss sensors	8,484	14
9.14.1	Instrumentation - Sampling ports - Carbon Steel	900	22
10.1.1	System Controls - PLC Units - PLC racks/power supplies	680	8
10.1.2	System Controls - PLC Units - CPUs	1,256	8
10.1.3	System Controls - PLC Units - I/O discrete input modules	614	8
10.1.4	System Controls - PLC Units - I/O discrete output modules	375	8
10.1.5	System Controls - PLC Units - I/O combination analog modules	5,874	8
10.1.6	System Controls - PLC Units - Ethernet modules	1,730	8
10.1.7	System Controls - PLC Units - Base expansion modules	118	8
10.1.8	System Controls - PLC Units - Base expansion controller modules	86	8
10.1.9	System Controls - PLC Units - UPSs	563	8
10.2.1	System Controls - Operator Equipment - Drive controllers	9,652	14
10.2.2	System Controls - Operator Equipment - Operator interface units	3,911	8
11.1.1	Building Structures and HVAC - Building 1 - Low Quality	118,890	37
11.4	Building Structures and HVAC - Concrete Pad	18,143	37
Indirect	Indirect and Add-On Costs (contingency from model)	305,971	37
	Process Cost	**518,789**	
	System Cost	**824,760**	
	O&M Cost	**198,657**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Mobilization and Demobilization	31,613
Construction Management and GC Overhead	41,579
Contingency	0
Process Engineering	103,758
Site Work	19,992
Yard Piping	3,418
Geotechnical	0
Standby Power	0
Electrical (including yard wiring)	38,176
Architectural Fees for Treatment Building	0
Pilot Study	1,330
Land Cost	2,444
Permits	1,407
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	51,879
Legal, Fiscal, and Administrative (2.0%)	10,376
Sales Tax (0.0%)	0
Financing during Construction (0.0%)	0

Breakdown of O&M costs	Annual Cost ($/year)
Manager (116 hrs/yr @ $45.2396/hr)	5,269
Administrative (116 hrs/yr @ $30.4776/hr)	3,550
Operator (1165 hrs/yr @ $31.9149/hr)	37,173
Materials for pretreatment (calculated as a percentage of capital)	346
Cartridge filter replacement (19 filters/yr @ $173.693/filter)	3,275
Materials for membrane process (calculated as a percentage of capital)	424
Membrane replacement (10 element/yr @ $564.7907/element)	5,809
Materials for cleaning (calculated as a percentage of capital)	305
Materials for feed water and booster pumps (calculated as a percentage of capital)	347

Breakdown of O&M costs	Annual Cost ($/year)
Facility maintenance (materials and labor) (1560 sf @ $5.7866/sf/yr)	9,027
Sulfuric Acid - Small Qty (23565 lbs/yr @ $0.3087/lb)	7,274
Antiscalant - Basic (2468 lbs/yr @ $1.8447/lb)	4,552
Membrane Cleaner - Low pH Sulfate Control (13 gal/yr @ $27.5474/gal)	349
Membrane Cleaner - High pH Detergent (13 gal/yr @ $31.6028/gal)	400
Energy for feed water and booster pumps (119 Mwh/yr @ $0.1212/kwh)	14,385
Energy for lighting (2 Mwh/yr @ $0.1212/kwh)	220
Energy for ventilation (3 Mwh/yr @ $0.1212/kwh)	363
POTW discharge fees (19757898 gal/yr @ $0.0044/gal)	87,493
Spent cartridge filter disposal (0 ton/yr @ $74.9152/ton)	23
Spent membrane element disposal (0 ton/yr @ $74.9152/ton)	14
Miscellaneous Allowance (0 @ $)	18,060

Reverse Osmosis / Nanofiltration, design 5.809 mgd, average 2.455 mgd, Mid-Cost Components, Feed Water: High Qual GW

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1	Membrane Process - Membrane Elements	679,514	N/A
1.2	Membrane Process - RO Pressure Vessels	224,291	22
1.3.1	Membrane Process - Feed Line Connectors - Victaulic, Galvanized	23,514	25
1.5.1	Membrane Process - Piping On Rack - Feed - Stainless Steel	121,348	45
1.5.2	Membrane Process - Piping On Rack - Permeate - PVC	5,132	45
1.5.3	Membrane Process - Piping On Rack - Concentrate - Stainless Steel	102,499	45
1.6	Membrane Process - Vessel Support Rack - Steel Beams	56,866	25
1.7	Membrane Process - Markup for Rack Assembly	299,601	29
2.1.1	Pretreatment Acid Tanks - Fiberglass	7,338	10
2.2.1	Pretreatment Antiscalant Tanks - Fiberglass	5,085	10
2.3.1	Cleaning Solution Makeup Tanks - Fiberglass	17,704	10
2.4.1	Cleaning Chemical Storage Tanks - Acid storage - Fiberglass	4,785	10
2.4.2	Cleaning Chemical Storage Tanks - High pH storage - Fiberglass	4,785	10
2.8.1	Acid Day Tanks - Fiberglass	4,891	10
2.9.1	Antiscalant Day Tanks - Fiberglass	4,710	10
2.10.1	Mixers for Antiscalant Storage Tanks - Mounted	1,717	25
2.11.1	Mixers for Antiscalant Day Tanks - Mounted	1,651	25
3.1.1	Inlet and Outlet Piping - CPVC	29,641	22
3.2.1	Cleaning System Piping - CPVC	3,430	22
3.3.1	Residuals Piping - CPVC	13,641	22
3.3.2	Residuals Piping - Excavation	1,508	22
3.3.3	Residuals Piping - Bedding	89	22
3.3.4	Residuals Piping - Backfill and Compaction	699	22
3.3.5	Residuals Piping - Thrust Blocks	2,153	22
4.1.1	Motor/Air Operated (on/off) Valves - Pretreatment acid - Stainless Steel	1,665	25
4.1.2	Motor/Air Operated (on/off) Valves - Antiscalant - Stainless Steel	1,665	25
4.1.3	Motor/Air Operated (on/off) Valves - Feed line - Cast Iron	36,483	25
4.1.4	Motor/Air Operated (on/off) Valves - Concentrate control - Stainless Steel	15,983	25
4.1.10	Motor/Air Operated (on/off) Valves - Cleaning - Stainless Steel	202,457	25
4.2.1	Manual Valves - Inlet and outlet - Cast Iron	6,852	25
4.3.1	Check Valves - Residuals - Cast Iron	2,870	25
4.3.2	Check Valves - Inlet - Cast Iron	6,754	25
4.3.4	Check Valves - Feed pumps - Cast Iron	15,822	25
4.3.5	Check Valves - Cleaning - Cast Iron	5,786	25
5.1.1	Acid Metering Pumps for Pretreatment - PVC - Electric	2,963	20
5.2.1	Antiscalant Metering Pumps for Pretreatment - Stainless Steel - Electric	3,304	20
5.4	Pumps - Feed Water	213,062	20
5.7	Pumps - Cleaning Pumps (separate for acid and caustic)	8,294	20
6.1	Screens and Filters - Cartridge Filters for Feed	203,680	35
6.2.1	Screens and Filters - Security Screens for Cleaning - Simplex Basket Screens	53,718	35
6.3	Screens and Filters - Cartridge Filters for Cleaning	123,757	35
8.1	Teflon Immersion Heaters for Cleaning Tanks	23,304	15
9.1.1	Instrumentation - Flow Meters - Inlet and Outlet - Venturi	37,666	15
9.2.1	Instrumentation - Flow Meters - Membrane Trains - Feed Line - Venturi	47,512	15
9.3.1	Instrumentation - Flow Meters - Membrane Trains - Permeate Line - Venturi	43,235	15
9.3.1	Instrumentation - Flow Meters - Membrane Trains - Concentrate Line - Venturi	37,488	15
9.4.1	Instrumentation - Flow Meters - Cleaning - Venturi	56,499	15
9.5.1	Instrumentation - Venturi	14,412	15
9.6	Instrumentation - Level Switches/Alarms (for cleaning tanks)	1,185	15
9.7	Instrumentation - High/Low Alarms (for pretreatment chemical tanks)	1,185	15

WBS #	Item	Total Cost ($)	Useful Life (yrs)
9.8	Instrumentation - High/Low Alarms (for cleaning chemical storage tanks)	1,185	15
9.1	Instrumentation - pH meters	10,530	15
9.11	Instrumentation - Temperature meters	1,780	15
9.12	Instrumentation - Conductivity meters	17,775	15
9.13	Instrumentation - Head loss sensors	14,848	15
9.14.1	Instrumentation - Sampling ports - Stainless Steel	8,700	35
10.1.1	System Controls - PLC Units - PLC racks/power supplies	1,020	10
10.1.2	System Controls - PLC Units - CPUs	1,256	10
10.1.3	System Controls - PLC Units - I/O discrete input modules	2,455	10
10.1.4	System Controls - PLC Units - I/O discrete output modules	375	10
10.1.5	System Controls - PLC Units - I/O combination analog modules	7,832	10
10.1.6	System Controls - PLC Units - Ethernet modules	1,730	10
10.1.7	System Controls - PLC Units - Base expansion modules	237	10
10.1.8	System Controls - PLC Units - Base expansion controller modules	171	10
10.1.9	System Controls - PLC Units - UPSs	563	10
10.2.1	System Controls - Operator Equipment - Drive controllers	16,087	15
10.2.2	System Controls - Operator Equipment - Operator interface units	920	10
10.2.3	System Controls - Operator Equipment - PC Workstations	2,013	10
10.2.4	System Controls - Operator Equipment - Printers - laser jet	627	10
10.2.5	System Controls - Operator Equipment - Printers - dot matrix	642	10
10.3.1	System Controls - Controls Software - Operator interface software	366	10
10.3.2	System Controls - Controls Software - PLC programming software	947	10
10.3.3	System Controls - Controls Software - PLC data collection software	1,380	10
10.3.4	System Controls - Controls Software - Plant intelligence software	22,960	10
11.1.1	Building Structures and HVAC - Building 1 - Medium Quality	419,822	40
11.1.2.1	Building Structures and HVAC - Building 1 - Heating System - Natural gas condensing furnace	61,640	25
11.4	Building Structures and HVAC - Concrete Pad	73,869	40
Indirect	Indirect and Add-On Costs (contingency from model)	1,857,320	40
	Process Cost	**3,455,924**	
	System Cost	**5,313,244**	
	O&M Cost	**2,017,479**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	**Total Cost ($)**
Mobilization and Demobilization	150,269
Construction Management and GC Overhead	192,949
Contingency	0
Process Engineering	360,983
Site Work	65,230
Yard Piping	13,803
Geotechnical	0
Standby Power	115,996
Electrical (including yard wiring)	252,677
Architectural Fees for Treatment Building	38,513
Pilot Study	64,004
Land Cost	11,857
Permits	3,530
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	345,592
Legal, Fiscal, and Administrative (2.0%)	69,118
Sales Tax (0.0%)	0
Financing during Construction (5.0%)	172,796

Breakdown of O&M costs	Annual Cost ($)
Manager (634 hrs/yr @ $57.6375/hr)	36,534
Administrative (634 hrs/yr @ $39.3563/hr)	24,946
Operator (6338 hrs/yr @ $35.9445/hr)	227,834
Materials for pretreatment (calculated as a percentage of capital)	2,083
Cartridge filter replacement (130 filters/yr @ $203.4792/filter)	26,510
Materials for membrane process (calculated as a percentage of capital)	6,795
Membrane replacement (165 element/yr @ $529.4913/element)	87,366
Materials for cleaning (calculated as a percentage of capital)	1,858
Materials for feed water and booster pumps (calculated as a percentage of capital)	2,131
Facility maintenance (materials and labor) (5090 sf @ $5.9193/sf/yr)	30,129
Sulfuric Acid - Small Qty (253899 lbs/yr @ $0.3087/lb)	78,367
Antiscalant - Basic (28052 lbs/yr @ $1.8447/lb)	51,749
Membrane Cleaner - Low pH Sulfate Control (203 gal/yr @ $27.5474/gal)	5,592
Membrane Cleaner - High pH Detergent (203 gal/yr @ $31.6028/gal)	6,415
Energy for feed water and booster pumps (1872 Mwh/yr @ $0.1212/kwh)	226,892
Energy for lighting (32 Mwh/yr @ $0.1212/kwh)	3,911
Energy for ventilation (13 Mwh/yr @ $0.1212/kwh)	1,547
Natural gas condensing furnace (23911 therms/yr @ $0.7941/therm)	18,987
POTW discharge fees (224932839 gal/yr @ $0.0044/gal)	994,106
Spent cartridge filter disposal (2 ton/yr @ $74.9152/ton)	154
Spent membrane element disposal (2 ton/yr @ $74.9152/ton)	165
Miscellaneous Allowance (0 @ $)	183,407

Reverse Osmosis / Nanofiltration, design 56.271 mgd, average 28.136 mgd, High-Cost Components, Feed Water: High Qual GW

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1	Membrane Process - Membrane Elements	4,612,457	N/A
1.2	Membrane Process - RO Pressure Vessels	1,522,459	22
1.3.1	Membrane Process - Feed Line Connectors - Victaulic, Galvanized	159,611	25
1.5.1	Membrane Process - Piping On Rack - Feed - Stainless Steel	823,697	45
1.5.2	Membrane Process - Piping On Rack - Permeate - PVC	34,835	45
1.5.3	Membrane Process - Piping On Rack - Concentrate - Stainless Steel	695,752	45
1.6	Membrane Process - Vessel Support Rack - Steel Beams	379,103	25
1.7	Membrane Process - Markup for Rack Assembly	2,026,759	29
2.1.1	Pretreatment Acid Tanks - Fiberglass	28,524	10
2.2.1	Pretreatment Antiscalant Tanks - Stainless Steel	11,510	35
2.3.1	Cleaning Solution Makeup Tanks - Stainless Steel	22,264	35
2.4.1	Cleaning Chemical Storage Tanks - Acid storage - Fiberglass	4,878	10
2.4.2	Cleaning Chemical Storage Tanks - High pH storage - Stainless Steel	4,710	35
2.8.1	Acid Day Tanks - Fiberglass	6,716	10
2.9.1	Antiscalant Day Tanks - Stainless Steel	4,880	35
2.10.1	Mixers for Antiscalant Storage Tanks - Mounted	2,412	25
2.11.1	Mixers for Antiscalant Day Tanks - Mounted	1,700	25
3.1.1	Inlet and Outlet Piping - Stainless Steel	136,508	45
3.2.1	Cleaning System Piping - Stainless Steel	24,848	45
3.3.1	Residuals Piping - Steel	74,713	35
3.3.2	Residuals Piping - Excavation	2,871	22
3.3.3	Residuals Piping - Bedding	144	22
3.3.4	Residuals Piping - Backfill and Compaction	1,331	22
3.3.5	Residuals Piping - Thrust Blocks	15,674	22
4.1.1	Motor/Air Operated (on/off) Valves - Pretreatment acid - Stainless Steel	1,665	25
4.1.2	Motor/Air Operated (on/off) Valves - Antiscalant - Stainless Steel	1,665	25
4.1.3	Motor/Air Operated (on/off) Valves - Feed line - Stainless Steel	685,694	25
4.1.4	Motor/Air Operated (on/off) Valves - Concentrate control - Stainless Steel	106,556	25
4.1.10	Motor/Air Operated (on/off) Valves - Cleaning - Stainless Steel	745,892	25
4.2.1	Manual Valves - Inlet and outlet - Cast Iron	22,996	25
4.3.1	Check Valves - Residuals - Stainless Steel	15,845	25
4.3.2	Check Valves - Inlet - Stainless Steel	37,737	25
4.3.4	Check Valves - Feed pumps - Stainless Steel	195,726	25
4.3.5	Check Valves - Cleaning - Stainless Steel	9,203	25
5.1.1	Acid Metering Pumps for Pretreatment - PVC - Motor Driven	8,099	20
5.2.1	Antiscalant Metering Pumps for Pretreatment - PVC - Motor Driven	6,078	20
5.4	Pumps - Feed Water	2,900,895	20
5.7	Pumps - Cleaning Pumps (separate for acid and caustic)	8,352	20
6.1	Screens and Filters - Cartridge Filters for Feed	1,569,824	35
6.2.1	Screens and Filters - Security Screens for Cleaning - Simplex Basket Screens	54,857	35
6.3	Screens and Filters - Cartridge Filters for Cleaning	126,670	35
8.1	Teflon Immersion Heaters for Cleaning Tanks	23,855	15
9.1.1	Instrumentation - Flow Meters - Inlet and Outlet - Orifice Plate	24,731	15
9.2.1	Instrumentation - Flow Meters - Membrane Trains - Feed Line - Magnetic	225,534	15
9.3.1	Instrumentation - Flow Meters - Membrane Trains - Permeate Line - Magnetic	225,534	15
9.3.1	Instrumentation - Flow Meters - Membrane Trains - Concentrate Line - Magnetic	136,649	15
9.4.1	Instrumentation - Flow Meters - Cleaning - Orifice Plate	13,941	15
9.5.1	Instrumentation - Magnetic	25,692	15
9.6	Instrumentation - Level Switches/Alarms (for cleaning tanks)	1,185	15
9.7	Instrumentation - High/Low Alarms (for pretreatment chemical tanks)	1,185	15

WBS #	Item	Total Cost ($)	Useful Life (yrs)
9.8	Instrumentation - High/Low Alarms (for cleaning chemical storage tanks)	1,185	15
9.1	Instrumentation - pH meters	10,530	15
9.11	Instrumentation - Temperature meters	1,780	15
9.12	Instrumentation - Conductivity meters	100,186	15
9.13	Instrumentation - Head loss sensors	99,691	15
9.14.1	Instrumentation - Sampling ports - Stainless Steel	58,450	35
10.1.1	System Controls - PLC Units - PLC racks/power supplies	4,422	10
10.1.2	System Controls - PLC Units - CPUs	1,256	10
10.1.3	System Controls - PLC Units - I/O discrete input modules	13,195	10
10.1.4	System Controls - PLC Units - I/O discrete output modules	750	10
10.1.5	System Controls - PLC Units - I/O combination analog modules	35,897	10
10.1.6	System Controls - PLC Units - Ethernet modules	1,730	10
10.1.7	System Controls - PLC Units - Base expansion modules	1,420	10
10.1.8	System Controls - PLC Units - Base expansion controller modules	1,028	10
10.1.9	System Controls - PLC Units - UPSs	563	10
10.2.1	System Controls - Operator Equipment - Drive controllers	45,042	15
10.2.2	System Controls - Operator Equipment - Operator interface units	920	10
10.2.3	System Controls - Operator Equipment - PC Workstations	4,026	10
10.2.4	System Controls - Operator Equipment - Printers - laser jet	627	10
10.2.5	System Controls - Operator Equipment - Printers - dot matrix	642	10
10.3.1	System Controls - Controls Software - Operator interface software	366	10
10.3.2	System Controls - Controls Software - PLC programming software	1,895	10
10.3.3	System Controls - Controls Software - PLC data collection software	2,761	10
10.3.4	System Controls - Controls Software - Plant intelligence software	45,920	10
10.3.5	System Controls - Controls Software - Early warning software	13,395	10
11.1.1	Building Structures and HVAC - Building 1 - High Quality	640,174	40
11.1.2.1	Building Structures and HVAC - Building 1 - Heating System - Natural gas condensing furnace	170,293	25
11.1.3.1	Building Structures and HVAC - Building 1 - Heating and Cooling System - Air conditioner	1,104,140	25
11.2.1	Building Structures and HVAC - Building 2 - High Quality	362,372	40
11.2.3.1	Building Structures and HVAC - Building 2 - Heating and Cooling System - Heat pump	4,053	25
11.3.1	Building Structures and HVAC - Building 3 - High Quality	1,286,225	40
11.3.2.1	Building Structures and HVAC - Building 3 - Heating System - Natural gas condensing furnace	27,051	25
11.3.3.1	Building Structures and HVAC - Building 3 - Cooling System - Air conditioner	7,126	25
11.4	Building Structures and HVAC - Concrete Pad	384,249	40
Indirect	Indirect and Add-On Costs (contingency from model)	10,347,182	40
	Process Cost	**22,207,784**	
	System Cost	**32,554,965**	
	O&M Cost	**19,273,680**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Mobilization and Demobilization	508,239
Construction Management and GC Overhead	858,411
Contingency	0
Process Engineering	1,620,601
Site Work	291,037
Yard Piping	88,455
Geotechnical	0
Standby Power	1,039,493
Electrical (including yard wiring)	1,709,688
Architectural Fees for Treatment Building	195,959
Pilot Study	132,875
Land Cost	110,762
Permits	16,337
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	2,220,778
Legal, Fiscal, and Administrative (2.0%)	444,156
Sales Tax (0.0%)	0
Financing during Construction (5.0%)	1,110,389

Breakdown of O&M costs	Annual Cost ($/year)
Manager (2379 hrs/yr @ $71.8488/hr)	170,939
Administrative (2379 hrs/yr @ $39.3563/hr)	93,634
Operator (23791 hrs/yr @ $43.8427/hr)	1,043,082
Materials for pretreatment (calculated as a percentage of capital)	15,790
Cartridge filter replacement (885 filters/yr @ $207.2116/filter)	183,293
Materials for membrane process (calculated as a percentage of capital)	46,125
Membrane replacement (1120 element/yr @ $529.4913/element)	593,030
Materials for cleaning (calculated as a percentage of capital)	1,899
Materials for feed water and booster pumps (calculated as a percentage of capital)	29,009
Facility maintenance (materials and labor) (22710 sf @ $5.9929/sf/yr)	136,098
Sulfuric Acid - Large Qty (2902863 lbs/yr @ $0.1107/lb)	321,406
Antiscalant - Basic (320728 lbs/yr @ $1.8447/lb)	591,654
Membrane Cleaner - Low pH Sulfate Control (1378 gal/yr @ $27.5474/gal)	37,958
Membrane Cleaner - High pH Detergent (1378 gal/yr @ $31.6028/gal)	43,546
Energy for feed water and booster pumps (21420 Mwh/yr @ $0.1212/kwh)	2,596,501
Energy for lighting (199 Mwh/yr @ $0.1212/kwh)	24,115
Energy for ventilation (90 Mwh/yr @ $0.1212/kwh)	10,902
Air conditioning (1878 Mwh/yr @ $0.1212/kwh)	227,680
Heat pump (15 Mwh/yr @ $0.1212/kwh)	1,760
Heat pump (43 Mwh/yr @ $0.1212/kwh)	5,236
Natural gas condensing furnace (80713 therms/yr @ $0.7941/therm)	64,091
POTW discharge fees (2553033230 gal/yr @ $0.0044/gal)	11,281,363
Spent cartridge filter disposal (11 ton/yr @ $74.9152/ton)	832
Spent membrane element disposal (21 ton/yr @ $74.9152/ton)	1,585
Miscellaneous Allowance (0 @ $)	1,752,153

Point of Use/Point of Entry, design 0.500 mgd, average 0.162 mgd, Contaminant: Perchlorate, Treatment Technology: POU Reverse Osmosis

WBS #	Item	Total Cost ($)	Useful Life (yrs)
23.1.1	Installed Treatment Equipment - POU/POE Unit Purchase	116,781	10
23.1.2	Installed Treatment Equipment - POU/POE Installation	41,270	10
23.1.3	Installed Treatment Equipment - Scheduling Time	7,330	N/A
23.2.1.1	Public Education - Technical Labor - Develop materials	319	N/A
23.2.1.3	Public Education - Technical Labor - Meetings	64	N/A
23.2.1.4	Public Education - Technical Labor - Post-meeting	64	N/A
23.2.2.1	Public Education - Clerical Labor - Develop materials	183	N/A
23.2.2.3	Public Education - Clerical Labor - Meetings	61	N/A
23.2.2.4	Public Education - Clerical Labor - Post-meeting	61	N/A
23.2.3.1	Public Education - Printed Material - Meeting flyers	8	N/A
23.2.3.2	Public Education - Printed Material - Meeting ads	60	N/A
23.2.3.4	Public Education - Printed Material - Meeting handouts	173	N/A
23.2.3.5	Public Education - Printed Material - Billing mailers	115	N/A
23.3.1	Initial Year Monitoring 1 - Sampling time	2,561	N/A
23.3.3	Initial Year Monitoring 1 - Analysis	35,074	N/A
23.3.4	Initial Year Monitoring 1 - Analysis (total coliform)	8,780	N/A
23.3.5	Initial Year Monitoring 1 - Shipping	598	N/A
Indirect	Indirect and Add-On Costs (contingency from model)	56,229	10
	Process Cost	**213,501**	
	System Cost	**269,730**	
	O&M Cost	**79,513**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Permitting	4,961
Pilot Testing	4,961
Legal	4,961
Engineering	24,807
Contingency	16,538

Breakdown of O&M costs	Annual Cost ($/year)
POU/POE Maintenance	9,978
Information updates	383
Maintenance Scheduling	9,529
Information updates	366
Sediment Pre-Filter	4,541
Pre-GAC Filter Cartridge	11,742
Post-GAC Filter Cartridge	6,785
RO Membrane	12,577
Billing mailers	173
Sampling time	1,277
Analysis	17,483
Shipping	304

Non-Treatment, design 0.500 mgd, average 0.162 mgd, Low-Cost Components, Design Type: Interconnection

WBS #	Item	Total Cost ($)	Useful Life (yrs)
3.1.1	Piping - Interconnect - PVC	59,800	17
3.1.2	Piping - Interconnect - Excavation	91,114	17
3.1.3	Piping - Interconnect - Backfill and Compaction	42,241	17
3.1.4	Piping - Interconnect - Asphalt Patch	12,713	17
4.1.1	Valves - Isolation (PRV) and Street - Ductile Iron	8,217	20
6.1.1	Instrumentation - Flow Meters - Interconnect - Propeller	4,141	14
Indirect	Indirect and Add-On Costs (contingency from model)	106,490	17
	Process Cost	**218,225**	
	System Cost	**324,716**	
	O&M Cost	**130,125**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Contingency	0
Process Engineering	43,645
Construction Management and GC Overhead	24,656
Site Work	0
Yard Piping	0
Geotechnical	0
Standby Power	0
Electrical (including yard wiring)	0
Mobilization and Demobilization	12,002
Architectural Fees for Treatment Building	0
Permits	0
Pilot Study	0
Land Cost	0
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	21,823
Legal, Fiscal, and Administrative (2.0%)	4,365
Sales Tax (0.0%)	0
Financing during Construction (0.0%)	0

Breakdown of O&M costs	Annual Cost ($/year)
Manager (0 hrs/yr @ $45.2396/hr)	4
Administrative (0 hrs/yr @ $31.9149/hr)	3
Operator (1 hrs/yr @ $30.4776/hr)	28
Purchased Water (59130 K gal @ $2K gal)	118,260
Miscellaneous Allowance (0 @ $)	11,830

Non-Treatment, design 0.500 mgd, average 0.162 mgd, Low-Cost Components, Design Type: New Well Construction

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1.1	Well Items - Well Casing - PVC	9,383	17
1.2.1	Well Items - Well screen - PVC Schedule 40	8,354	17
1.3.1	Well Items - Plugs - PVC	172	17
1.4	Well Items - Well Drilling	22,988	N/A
1.5	Well Items - Gravel Pack	14,275	N/A
1.6	Well Items - Well Development	875	N/A
1.7	Well Items - Surface seal well, concrete fill	5,125	N/A
3.2.1	Piping - Well - PVC	615	17
3.2.2	Piping - Well - Excavation	4,556	17
3.2.3	Piping - Well - Backfill and Compaction	2,112	17
4.2.2	Valves - Motor/Air Operated (on/off) - Well Pump - Polypropylene/PVC	1,282	20
5.2	Pumps - Well Pump	14,343	17
6.2.1	Instrumentation - Flow Meters - Well - Propeller	4,141	14
8.1.1	Building Structures - Building 1 - Small Low Cost Shed	9,200	20
Indirect	Indirect and Add-On Costs (contingency from model)	110,111	17
	Process Cost	**97,419**	
	System Cost	**207,530**	
	O&M Cost	**38,061**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Contingency	0
Process Engineering	19,484
Construction Management and GC Overhead	12,509
Site Work	2,563
Yard Piping	0
Geotechnical	27,008
Standby Power	0
Electrical (including yard wiring)	8,822
Mobilization and Demobilization	7,278
Architectural Fees for Treatment Building	0
Permits	0
Pilot Study	0
Land Cost	20,757
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	9,742
Legal, Fiscal, and Administrative (2.0%)	1,948
Sales Tax (0.0%)	0
Financing during Construction (0.0%)	0

Breakdown of O&M costs	Annual Cost ($/year)
Manager (4 hrs/yr @ $45.2396/hr)	193
Administrative (4 hrs/yr @ $31.9149/hr)	136
Operator (43 hrs/yr @ $30.4776/hr)	1,298
Facility maintenance (materials and labor) (200 sf @ $5.7866/sf/yr)	1,157
Well pump (calculated as a percentage of capital)	143
Energy for well pumps (261 Mwh/yr @ $0.1212/kwh)	31,674
Miscellaneous Allowance (0 @ $)	3,460

Non-Treatment, design 1.000 mgd, average 0.350 mgd, Mid-Cost Components, Design Type: Interconnection

WBS #	Item	Total Cost ($)	Useful Life (yrs)
3.1.1	Piping - Interconnect - PVC	59,800	22
3.1.2	Piping - Interconnect - Excavation	91,114	22
3.1.3	Piping - Interconnect - Backfill and Compaction	42,241	22
3.1.4	Piping - Interconnect - Asphalt Patch	12,713	22
4.1.1	Valves - Isolation (PRV) and Street - Ductile Iron	8,217	25
6.1.1	Instrumentation - Flow Meters - Interconnect - Venturi	12,496	15
Indirect	Indirect and Add-On Costs (contingency from model)	101,239	22
	Process Cost	**226,580**	
	System Cost	**327,819**	
	O&M Cost	**281,089**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Contingency	0
Process Engineering	27,190
Construction Management and GC Overhead	25,561
Site Work	0
Yard Piping	0
Geotechnical	0
Standby Power	0
Electrical (including yard wiring)	0
Mobilization and Demobilization	9,970
Architectural Fees for Treatment Building	0
Permits	0
Pilot Study	0
Land Cost	0
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	22,658
Legal, Fiscal, and Administrative (2.0%)	4,532
Sales Tax (0.0%)	0
Financing during Construction (5.0%)	11,329

Breakdown of O&M costs	Annual Cost ($/year)
Manager (0 hrs/yr @ $51.7408/hr)	5
Administrative (0 hrs/yr @ $34.0506/hr)	3
Operator (1 hrs/yr @ $30.4776/hr)	28
Purchased Water (127750 K gal @ $2K gal)	255,500
Miscellaneous Allowance (0 @ $)	25,554

Non-Treatment, design 1.000 mgd, average 0.350 mgd, Mid-Cost Components, Design Type: New Well Construction

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1.1	Well Items - Well Casing - Stainless Steel	246,420	45
1.2.1	Well Items - Well screen - PVC Schedule 40	16,708	22
1.3.1	Well Items - Plugs - PVC	343	22
1.4	Well Items - Well Drilling	45,975	N/A
1.5	Well Items - Gravel Pack	28,550	N/A
1.6	Well Items - Well Development	1,750	N/A
1.7	Well Items - Surface seal well, concrete fill	10,250	N/A
3.2.1	Piping - Well - PVC	1,230	22
3.2.2	Piping - Well - Excavation	9,111	22
3.2.3	Piping - Well - Backfill and Compaction	4,224	22
4.2.2	Valves - Motor/Air Operated (on/off) - Well Pump - Cast Iron	9,920	25
5.2	Pumps - Well Pump	28,686	20
6.2.1	Instrumentation - Flow Meters - Well - Venturi	12,496	15
8.1.1	Building Structures - Building 1 - Small Low Cost Shed	18,401	25
Indirect	Indirect and Add-On Costs (contingency from model)	380,036	45
	Process Cost	**434,064**	
	System Cost	**814,100**	
	O&M Cost	**76,202**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Contingency	0
Process Engineering	52,088
Construction Management and GC Overhead	35,031
Site Work	5,126
Yard Piping	0
Geotechnical	54,017
Standby Power	51,369
Electrical (including yard wiring)	41,566
Mobilization and Demobilization	25,182
Architectural Fees for Treatment Building	1,656
Permits	0
Pilot Study	0
Land Cost	40,210
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	43,406
Legal, Fiscal, and Administrative (2.0%)	8,681
Sales Tax (0.0%)	0
Financing during Construction (5.0%)	21,703

Breakdown of O&M costs	Annual Cost ($/year)
Manager (9 hrs/yr @ $51.7408/hr)	441
Administrative (9 hrs/yr @ $34.0506/hr)	290
Operator (85 hrs/yr @ $30.4776/hr)	2,596
Facility maintenance (materials and labor) (400 sf @ $5.7866/sf/yr)	2,315
Well pump (calculated as a percentage of capital)	287
Energy for well pumps (523 Mwh/yr @ $0.1212/kwh)	63,347
Miscellaneous Allowance (0 @ $)	6,927

Non-Treatment, design 3.536 mgd, average 1.417 mgd, High-Cost Components, Design Type: Interconnection

WBS #	Item	Total Cost ($)	Useful Life (yrs)
3.1.1	Piping - Interconnect - PVC	177,500	22
3.1.2	Piping - Interconnect - Excavation	103,262	22
3.1.3	Piping - Interconnect - Backfill and Compaction	47,873	22
3.1.4	Piping - Interconnect - Asphalt Patch	14,408	22
4.1.1	Valves - Isolation (PRV) and Street - Ductile Iron	20,394	25
6.1.1	Instrumentation - Flow Meters - Interconnect - Magnetic	11,277	15
Indirect	Indirect and Add-On Costs (contingency from model)	173,295	22
	Process Cost	**374,714**	
	System Cost	**548,009**	
	O&M Cost	**1,137,900**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Contingency	17,763
Process Engineering	44,966
Construction Management and GC Overhead	30,378
Site Work	0
Yard Piping	0
Geotechnical	0
Standby Power	0
Electrical (including yard wiring)	0
Mobilization and Demobilization	16,487
Architectural Fees for Treatment Building	0
Permits	0
Pilot Study	0
Land Cost	0
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	37,471
Legal, Fiscal, and Administrative (2.0%)	7,494
Sales Tax (0.0%)	0
Financing during Construction (5.0%)	18,736

Breakdown of O&M costs	Annual Cost ($/year)
Manager (0 hrs/yr @ $57.6375/hr)	5
Administrative (0 hrs/yr @ $35.9445/hr)	3
Operator (1 hrs/yr @ $39.3563/hr)	36
Purchased Water (517205 K gal @ $2K gal)	1,034,410
Miscellaneous Allowance (0 @ $)	103,445

Non-Treatment, design 3.536 mgd, average 1.417 mgd, High-Cost Components, Design Type: New Well Construction

WBS #	Item	Total Cost ($)	Useful Life (yrs)
1.1.1	Well Items - Well Casing - Stainless Steel	616,050	45
1.2.1	Well Items - Well screen - PVC Schedule 40	41,769	22
1.3.1	Well Items - Plugs - PVC	858	22
1.4	Well Items - Well Drilling	114,938	N/A
1.5	Well Items - Gravel Pack	71,375	N/A
1.6	Well Items - Well Development	4,375	N/A
1.7	Well Items - Surface seal well, concrete fill	25,625	N/A
3.2.1	Piping - Well - PVC	3,075	22
3.2.2	Piping - Well - Excavation	22,778	22
3.2.3	Piping - Well - Backfill and Compaction	10,560	22
4.2.2	Valves - Motor/Air Operated (on/off) - Well Pump - Stainless Steel	53,278	25
5.2	Pumps - Well Pump	85,420	20
6.2.1	Instrumentation - Flow Meters - Well - Magnetic	6,832	15
8.1.1	Building Structures - Building 1 - Low Quality	79,569	40
Indirect	Indirect and Add-On Costs (contingency from model)	948,179	45
	Process Cost	**1,136,501**	
	System Cost	**2,084,680**	
	O&M Cost	**236,470**	
	Totals are computed before component costs are rounded		

Breakdown of indirect and add-on costs	Total Cost ($)
Contingency	58,752
Process Engineering	136,380
Construction Management and GC Overhead	75,554
Site Work	12,815
Yard Piping	0
Geotechnical	135,042
Standby Power	101,216
Electrical (including yard wiring)	105,693
Mobilization and Demobilization	64,197
Architectural Fees for Treatment Building	7,161
Permits	854
Pilot Study	0
Land Cost	57,309
Installation, Transportation, and O&P (0.0%)	0
Instrumentation and Control (0.0%)	0
Miscellaneous Allowance (10.0%)	113,650
Legal, Fiscal, and Administrative (2.0%)	22,730
Sales Tax (0.0%)	0
Financing during Construction (5.0%)	56,825

Breakdown of O&M costs	Annual Cost ($/year)
Manager (21 hrs/yr @ $57.6375/hr)	1,227
Administrative (21 hrs/yr @ $35.9445/hr)	765
Operator (213 hrs/yr @ $39.3563/hr)	8,380
Facility maintenance (materials and labor) (1000 sf @ $5.7866/sf/yr)	5,787
Well pump (calculated as a percentage of capital)	854
Energy for well pumps (1633 Mwh/yr @ $0.1212/kwh)	197,960
Miscellaneous Allowance (0 @ $)	21,497

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Perchlorate Occurrence and Monitoring Report

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Office of Water
EPA-HQ-OW-2018-0780
April 2019
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Executive Summary

On February 11, 2011 (76 FR 7762; USEPA, 2011a), the United States Environmental Protection Agency (EPA) announced its decision to regulate perchlorate under the Safe Drinking Water Act (SDWA) based on its finding that perchlorate meets the SDWA's three criteria for regulating a contaminant: 1) the contaminant may have an adverse effect on the health of persons, 2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems (PWSs) with a frequency and at levels of public health concern, and 3) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

EPA is proposing a Maximum Contaminant Level Goal (MCLG) and a National Primary Drinking Water Regulation (NPDWR) for control of perchlorate in PWSs. In accordance with Section 1412(b)(3)(c) of SDWA, EPA must prepare a Health Risk Reduction and Cost Analysis (HRRCA) of the proposed Maximum Contaminant Level (MCL) and alternative MCLs. The HRRCA must assess the quantifiable and non-quantifiable costs that are likely to occur as a result of compliance with the MCL. These costs could be for new treatment processes as well as incremental monitoring and administrative costs. EPA must also provide an estimate of the health risk reduction benefits likely to occur as a result of the treatment to comply with each perchlorate concentration level assessed. System customers will benefit from health risk reductions associated with lower contaminant exposure levels.

EPA evaluated the available peer-reviewed science and supporting studies, as well as data collected by accepted methods on the national occurrence of perchlorate in drinking water. EPA determined that the data from the Unregulated Contaminant Monitoring Rule 1 (UCMR 1) are the best available nationally representative data for characterizing the frequency and levels of perchlorate occurrence in public drinking water systems. The UCMR 1 perchlorate monitoring of drinking water – a census of large PWSs (serving more than 10,000 people) and a nationally representative statistical sample of small systems (serving 10,000 people or fewer) – represents the most extensive, nationally representative monitoring program for perchlorate in public drinking water systems. PWSs conducted UCMR 1 monitoring for perchlorate in drinking water between 2001 and 2005. EPA used UCMR 1 data to estimate the national occurrence of perchlorate in public drinking water systems. To support this analysis, EPA also reviewed state-sponsored studies (including Arizona, California, Iowa, Maryland, Massachusetts, Nevada, New Jersey and Texas) and other drinking water occurrence data (including American Water Works Association Research Foundation, American Water System Survey, Consumer Confidence Reports and the Environmental Working Group).

Occurrence analyses based on this UCMR 1 Perchlorate Dataset identify analytical detections in PWSs located in 26 states and 2 territories. Analytical detections of perchlorate at or above 4 µg/L were identified in 1.58% (540) of the 34,132 UCMR 1 perchlorate samples. An estimated 4.60% of large PWSs (141 large systems) serving approximately 16.2 million people reported at least one detection of perchlorate at or above 4 µg/L and 1.0% of small PWSs (8 small systems) serving approximately 13,000 people reported perchlorate detections at or above 4 µg/L. The percentage of ground water and surface water PWSs reporting perchlorate detections is about the same. While perchlorate analytical detections are fairly numerous and widespread

geographically, the UCMR 1 findings indicate that perchlorate occurs at relatively low levels. Fifteen systems had detections of perchlorate greater than 18 µg/L; two systems had detections of perchlorate greater than 56 µg/L.

Exhibit ES-1. Systems and Populations with at least One Detection Relative to Select Thresholds Based on the updated UCMR 1 Perchlorate Dataset

System Type	Total Number of Systems in UCMR 1	Total Pop. Served by Systems in UCMR 1	Systems with at least one detection > threshold					
			≥ 4 µg/L		> 18 µg/L		> 56 µg/L	
			Number of Systems	Pop. Served by Systems	Number of Systems	Pop. Served by Systems	Number of Systems	Pop. Served by Systems
Small Systems (serving ≤10,000)	797	2,760,570	8	13,483	1	4,309	0	0
Large Systems (serving >10,000)	3,068	222,853,101	141	16,159,082	14	696,871	2	64,733
All Systems	**3,865**	**225,613,671**	**149**	**16,172,565**	**15**	**701,180**	**2**	**64,733**

[1] The UCMR 1 minimum reporting level (MRL) for perchlorate was equal to 4 µg/L. Thus, assessments relative to the threshold of greater than or equal to 4 µg/L served to identify all perchlorate sample detections in UCMR 1.

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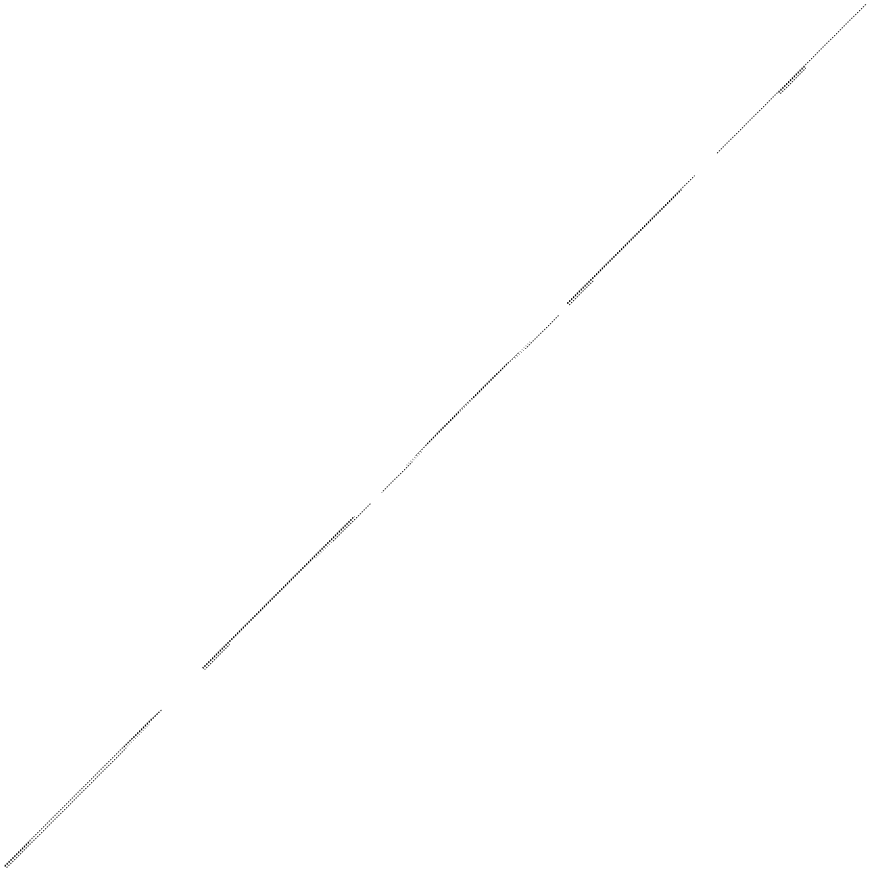

Exhibits

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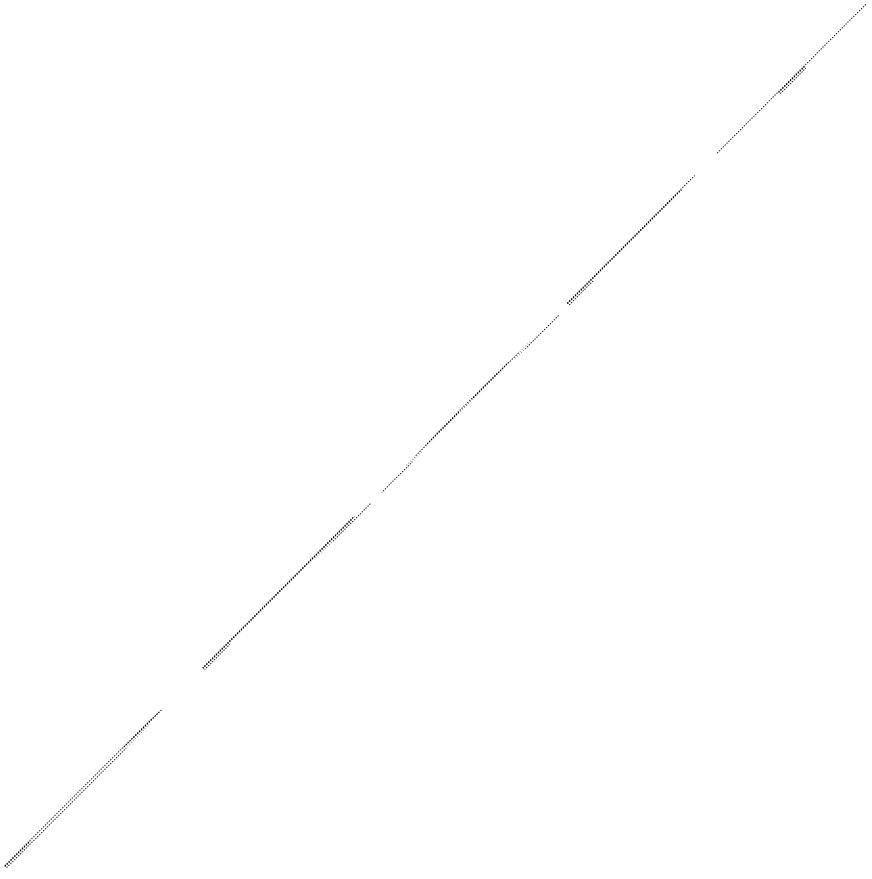

Appendices

Appendix A: Occurrence in Ambient Water and in Drinking Water (from Sources Other than UCMR 1)

Appendix B: A Review of Perchlorate Occurrence in California Public Drinking Water Systems: 1994-2011

Appendix C: Data Quality Considerations from the Chamber of Commerce

Appendix D: UCMR 1 Perchlorate Detections with Source Water Detection Categories Identified

Appendix E: UCMR 1 (June 2013 Version) State-Level Occurrence Measures

Abbreviations

ADEQ	Arizona Department of Environmental Quality
AMS	Alfred Merritt Smith Treatment Plant
ASTSWMO	Association of State and Territorial Solid Waste Management Officials
ATSDR	Agency for Toxic Substances and Disease Registry
AWS	American Water System
AWWA	American Water Works Association
AwwaRF	American Water Works Association Research Foundation
CA EPA	California Environmental Protection Agency
CA OEHHA	California's Office of Environmental Health Hazard Assessment
CA UCRM	California's Unregulated Chemicals Requiring Monitoring
CAP	Central Arizona Project
CASRN	Chemical Abstract Services Registry Number
CCL	Contaminant Candidate List
CCR	Consumer Confidence Report
CDHS	California Department of Health Services
CDPH	California Department of Public Health
CWS	Community Water System
DL	Detection Limit
DQO	Data Quality Objective
DWP	Drinking Water Program
EP	Entry Point
EPA	Environmental Protection Agency
EPA STORET	EPA Storage and Retrieval (Data Warehouse)
EWG	Environmental Working Group
HRRCA	Health Risk Reduction and Cost Analysis
IA SWRL	Iowa Statewide Rural Well Water Survey
IC	Ion Chromatography
LC	Liquid Chromatography
LCMRL	Lowest Concentration Minimum Reporting Level
LIWC	Long Island Water Conference
MassDEP	Massachusetts Department of Environmental Protection

MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MDL	Method Detection Limit
MEG	Maximum Exposure Guidelines
MRL	Minimum Reporting Level
MS	Mass Spectrometry
MWD	Metropolitan Water District
NAWQA	National Water-Quality Assessment
NDEP	Nevada Division of Environmental Protection
NHANES	National Health and Nutrition Examination Survey
NJDEP	New Jersey Department of Environmental Protection
NJDWQI	New Jersey Drinking Water Quality Institute
NMED	New Mexico Environment Department
NPDWR	National Primary Drinking Water Regulation
NRC	National Research Council
NTNCWS	Non-Transient Non-Community Water System
NWIS	National Water Information System
OGWDW	Office of Ground Water and Drinking Water
PHG	Public Health Goal
PPM	Parts Per Million
PSV	Preliminary Screening Values
PWS	Public Water System
PWSID	Public Water System Identification Number
QA	Quality Assurance
QAPP	Quality Assurance Project Plan
QC	Quality Control
RL	Reporting Level
RM	River Mountains Treatment Plant
RSD	Relative Standard Deviation
SCDHS	Suffolk County Department of Health Service
SCWA	Suffolk County Water Authority
SDWA	Safe Drinking Water Act

SIM	Selective Ion Monitoring
SNWS	Southern Nevada Water System
SR	Source Water
TCEQ	Texas Commission on Environmental Quality
TDS	Total Dissolved Solids
TNCWS	Transient Non-Community Water System
TRI	Toxics Release Inventory
UCMR 1	Unregulated Contaminant Monitoring Rule 1
USGAO	United States Government Accountability Office
USGS	United States Geological Survey
WaterRF	Water Research Foundation
WSSC	Washington Suburban Sanitary Commission

1 Introduction

This occurrence and monitoring report describes the data and analyses used by the U.S. Environmental Protection Agency (EPA) to develop national estimates of perchlorate occurrence in public drinking water systems. Additional supplemental perchlorate occurrence background information and data were also reviewed. The information, data, and analyses described in this report are organized into six chapters and five appendices with a brief description of each chapter and appendix presented below.

- **Chapter 1: The Introduction** provides the regulatory history of perchlorate in the context of public drinking water and a summary of state drinking water standards and guidance levels.

- **Chapter 2: Perchlorate Background** provides information on perchlorate chemical and physical properties, sources of perchlorate, environmental fate, and laboratory analytical methods.

- **Chapter 3: Perchlorate Occurrence Data from the Unregulated Contaminant Monitoring Rule 1 (UCMR 1)** presents background information on the UCMR 1 Perchlorate Dataset, as well as the quality assurance / quality control (QA/QC) review of those data.

- **Chapter 4: Analysis of the UCMR 1 Occurrence Data** discusses the non-parametric approach for analyzing the occurrence data and presents results based on that analysis.

- **Chapter 5: Laboratory Analytical Methods** discusses the analytical methods used in the identification and quantification of perchlorate in drinking water.

- **Chapter 6: References** is a list of the cited and supporting scientific literature used in development of the document.

- **Appendix A** presents occurrence data compiled by states and other organizations for perchlorate from a variety of ambient water and non-UCMR 1 drinking water sources.

- **Appendix B** presents a detailed description and characterization of the perchlorate occurrence data provided by the State of California.

- **Appendix C** provides a summary of considerations for additional data quality measures related to comments from the Chamber of Commerce, as well as a comparison of current perchlorate data from the State of California with California UCMR 1 perchlorate data.

- **Appendix D** presents the public water system inventory and other background details regarding UCMR 1 perchlorate detections from source water samples and samples from entry points to the distribution systems as discussed in Section 3.4.2.

- **Appendix E** provides a summary of monitoring results and occurrence analyses by state based on the UCMR 1 Perchlorate Dataset (June 2013 Version).

1.1 SDWA Statutory Requirements and Rulemaking Process for Perchlorate in Drinking Water

The Safe Drinking Water Act (SDWA) Sections 1412(b)(1)-(6) and (15) describe requirements for regulating drinking water contaminants. The United States Environmental Protection Agency (EPA) included perchlorate on the first, second, and third Contaminant Candidate Lists (CCLs) that were published in the *Federal Register* on March 2, 1998, February 24, 2005, and October 8, 2009, respectively (USEPA, 1998; USEPA, 2005a; USEPA, 2009a). On May 1, 2007, EPA published an update on the agency's evaluation of perchlorate as part of the preliminary regulatory determination for 11 other CCL 2 contaminants (72 FR 24016; USEPA, 2007a). The agency did not make a preliminary determination for perchlorate as part of this notice. However, the agency requested public comment on the information included in the notice and on the options that the agency was evaluating, it also requested information that could assist the agency in its decision-making process.

On October 10, 2008, EPA published a preliminary regulatory determination for perchlorate (73 FR 60262; USEPA, 2008a), requesting public comment on its determination that development of a National Primary Drinking Water Regulation (NPDWR) for perchlorate would not present a meaningful opportunity for health risk reduction for persons served by public water systems (PWSs). The October 2008 notice describes in detail EPA's basis for its preliminary regulatory determination.

On January 8, 2009, EPA (USEPA, 2009b) announced that it was seeking advice from the National Academy of Sciences (NAS) before making a final determination on whether to issue a national regulation for perchlorate in drinking water. In conjunction with that announcement, EPA also issued an interim health advisory of 15 parts per billion (ppb or µg/L) to assist state and local officials in addressing local contamination of perchlorate in drinking water and making a corresponding change to the factors considered in cleaning up Superfund sites.

On August 19, 2009 (74 FR 41883; USEPA, 2009c), EPA published the *Perchlorate Supplemental Request for Comments* and stated that it was not, at that time, planning to request additional National Research Council (NRC) review of issues related to perchlorate. Instead, EPA requested comment on additional approaches to analyzing data related to EPA's perchlorate regulatory determination. These additional comments were sought in an effort to ensure consideration of all potential options for evaluating whether there is a meaningful opportunity for human health risk reduction of perchlorate through an NPDWR. EPA stated that the alternative analyses (e.g., alternative health reference levels based on body weight and water consumption of 12 life stages ranging from birth to less than 21 years old) presented in the notice could lead the agency to make a determination to regulate perchlorate.

On February 11, 2011 (76 FR 7762; USEPA, 2011a), EPA announced its decision to regulate perchlorate under the SDWA based on its finding that perchlorate meets the SDWA's three criteria for regulating a contaminant: 1) the contaminant may have an adverse effect on the health of persons, 2) the contaminant is known to occur or there is a substantial likelihood that

the contaminant will occur in PWSs with a frequency and at levels of public health concern, and 3) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

On May 29, 2013, the EPA Science Advisory Board (SAB) recommended that EPA, as part of its development of a regulation for perchlorate, derive a perchlorate Maximum Contaminant Level Goal (MCLG) through the use of a physiologically-based pharmacokinetic/ pharmacodynamic model based upon perchlorate's mode of action regarding human health. The findings of this modeling are to be applied toward the development of a Maximum Contaminant Level (MCL). EPA collaborated with the Food and Drug Administration to implement the SAB recommendations and conduct the modeling.

To address the SAB recommendations, EPA created a BBDR models that predicts changes in thyroid hormone levels as a result of nutritional iodine intake and perchlorate exposure in women prior to pregnancy and early gestation. These models were peer reviewed in January 2017[4]. Reviewers stressed the importance of developing an early pregnancy model when considering adverse neurodevelopmental impacts. EPA responded to this peer review by developing an early pregnancy model and updated key parameters for that model.

EPA carried out a subsequent peer review January 2018 to evaluate updates to the BBDR model and presented the alternative approaches that link the revised perchlorate BBDR model predictions to neurodevelopmental effects. The January 2018 peer review was largely supportive of the efforts described in EPA's report titled "Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water"

When proposing an MCL, EPA must publish, and seek comment on, the Health Risk Reduction and Cost Analysis (HRRCA) of each alternative MCL considered (SDWA Section 1412(b)(3)(C)(i)). This includes the quantifiable and non-quantifiable benefits from reductions in health risk, including those from removing co-occurring contaminants (not counting the benefits resulting from compliance with other proposed or final regulations); costs of compliance (not counting costs resulting from other regulations); any increased health risks (including those from co-occurring contaminants) that may result from compliance; and incremental costs and benefits of each alternative MCL considered.

Once EPA makes a determination to regulate a contaminant in drinking water, SDWA Section 1412(b)(1)(E) requires that EPA issue a proposed NPDWR within 24 months and a final NPDWR within 18 months after the proposal (the statute allows a nine-month extension of this promulgation date).

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[4] *Biologically Based Dose Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analysis.* The report is available through the docket at [HYPERLINK "http://www.regulations.gov"] **(Docket ID No. EPA-HQ-OW-2016-0439).**

1.2 State Standards and Guidelines for Perchlorate in Drinking Water

There also have been state actions on perchlorate standards, guidelines, and advisories. In 2006, Massachusetts adopted a drinking water standard for perchlorate of 2 µg/L, and in 2007, California promulgated a drinking water standard of 6 µg/L.[5] Other states have established non-enforceable guidance levels, action or advisory levels. [REF _Ref366605281 * MERGEFORMAT] presents a summary of the state standards and guidance levels for perchlorate in drinking water and [REF _Ref366605289 * MERGEFORMAT] presents a summary of the state guidance levels for perchlorate in ground water. Depending on the state, a particular level may require a PWS to notify the public, serve as a screening tool for further action, or guide clean-up actions.

Exhibit [SEQ Exhibit * ARABIC]: Summary of State Standards and Guidance Levels for Perchlorate in Drinking Water

State	Level (µg/L)	Description
State Drinking Water Standards		
California	6	Existing MCL
Massachusetts	2	Existing MCL
State Drinking Water Guidance, Action or Advisory Levels[1,2,3]		
Arizona	14	Health-based guidance level (USEPA Region 9, 2016)
Hawaii	26	Action level for drinking water (HI DOH, 2011)
Maine	0.8	Maximum Exposure Guidelines (MEG) for Drinking Water (ME DHHS, 2016)
Maryland	1	Advisory Level (ASTSWMO, 2011; Harford County Government, 2007)
Nevada	18	Provisional action level based upon EPA guidance (NDEP, 2012)
New Jersey	5	Interim Ground Water Quality Criteria (NJ DEP, 2016)
New Mexico	1	Drinking Water Guidance Level (ASTSWMO, 2011)
	13.8	Tap water screening level (NMED, 2014)
New York	5	Drinking Water Planning Level (ASTSWMO, 2011)
	18	State Guidance Level (NY DOH, 2010)
Oregon	4	Recommended Action Level (OR DHS, 2004)
Vermont	4	Interim enforcement standard (ASTSWMO, 2011)

Adapted from the United States Government Accountability Office (USGAO) (2010) and Association of State and Territorial Solid Waste Management Officials (ASTSWMO) (2011).

[1] A "Preliminary Screening Value" (PSV) of 24.5 µg/L in Alabama had been cited in ASTSWMO (2011). However, that value can no longer be verified.

[2] A "drinking water threshold level" and "interim action level" of 4 µg/L in Kansas and Texas, respectively, had been cited in USGAO (2010). However, these values can no longer be verified.

[5] In January 2011, the State of California proposed a Public Health Goal (PHG) of 1 µg/L for perchlorate. The existing California MCL is based on an earlier California 2004 PHG of 6 µg/L (CA EPA, 2011). In December 2012, CA's Office of Environmental Health Hazard Assessment (CA OEHHA) released a revised draft technical support document for the [HYPERLINK "http://www.oehha.ca.gov/water/phg/120712Perchlorate.html"] (CA EPA, 2012).

[3] In a self-published, non-peer-reviewed study by Integral Consulting (2016), additional and/or updated state advisories for perchlorate were noted, including: Iowa, with an advisory level of 4.9 µg/L; New Hampshire, with a public health goal of 1 µg/L and; Vermont, with an advisory level of 2.2 µg/L. These advisories are not included on the drinking water-related websites of these three states.

Exhibit [SEQ Exhibit * ARABIC]: **Summary of State Guidance Levels for Perchlorate in Ground Water**

State	Level (µg/L)	Description
State Guidance, Action or Advisory Levels for Perchlorate in Ground Water[1]		
Alaska	14	Groundwater clean-up level for ammonium perchlorate (AK DEC, 2017)
	26	Groundwater clean-up level for perchlorate (AK DEC, 2009)
Florida	4	Clean-up target level for potable water (*This level, established in regulation, is not a standard but serves as a default level for contaminated site clean-ups. Alternative levels may be used where there is sufficient site-specific information.*) (FL Department of the State, 2005)
	40	Clean-up target level for ground water of low yield or poor quality (*This level, established in regulation, is not a standard but serves as a default level for contaminated site clean-ups. Alternative levels may be used where there is sufficient site-specific information.*) (FL Department of the State, 2005)
Hawaii	26	Action levels for ground water that could be a source of drinking water (HI DOH, 2011)
	600	Action levels for ground water not used as a source of drinking water (HI DOH, 2011)
Iowa	15	Statewide Standards for a Protected Groundwater Source (IA DNR, 2016)
	75	Statewide Standards for an Unprotected Groundwater Source (IA DNR, 2016)
Kansas	10.9	Default risk-based clean-up level for residential or drinking water pathway (*based on established equations and current EPA reference dose*) (KDHE, 2010)
	70.9	Default risk-based clean-up level for nonresidential pathway (*based on established equations and current EPA reference dose*) (KDHE, 2010)
Maryland	2.6	Groundwater clean-up standards for Type I and II Aquifers (MDE, 2008)
Missouri	10.9	Groundwater Target Concentrations at Point of Exposure (MO DNR, 2006)
Nebraska	6.4	Voluntary Clean-up Program Remediation Goals (NDEQ, 2012)
Nevada	18	Provisional action level used as default clean-up level for all ground water (NDEP, 2012)
New Mexico	4-18	Ground water clean-up level (NMED, 2004)
Texas	17	Protective clean-up level for residential land use (TCEQ, 2016)
	51	Protective clean-up level for industrial/commercial land use (TCEQ, 2016)
Vermont	2	Interim preventive action level (VT DEC, 2015)
	4	Interim enforcement standard; interim groundwater quality standard. (*This level is considered guidance, despite its being termed a "standard."*) (VT DEC, 2015)
Wisconsin	0.1	Public health ground water quality standard -- preventive action limit (WI Administrative Code, 2017)
	1	Public health ground water quality standard -- enforcement standard (WI Administrative Code, 2017)

Adapted from USGAO (2010) and ASTSWMO (2011).

[1] A "Preliminary Screening Value" (PSV) of 24.5 µg/L in Alabama had been cited in ASTSWMO (2011). However, that value can no longer be verified.

2 Perchlorate Background

This section summarizes background on perchlorate including its chemical and physical properties; sources; environmental fate and transport of the perchlorate ion; and laboratory analytical methods.

2.1 Chemical and Physical Properties

Perchlorate is an inorganic chemical containing one chlorine atom bound to four oxygen atoms in a tetrahedral configuration (see [REF _Ref366605356]). As such, perchlorates (ClO_4^-) are a group of anions that form salts with most cations.

Exhibit [SEQ Exhibit * ARABIC]: Chemical Structure of Perchlorate

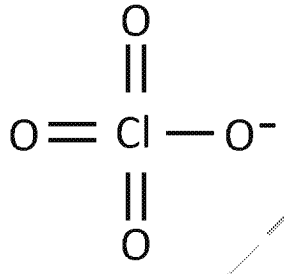


Figure based on information from the Hazardous Substances Data Bank (HSDB), 2012.

Commonly used perchlorate salts include ammonium perchlorate and potassium perchlorate. Perchlorate is also used as a component of sodium perchlorate, aluminum perchlorate, hydrazine perchlorate, hydrogen perchlorate, hydroxylammonium perchlorate, lithium perchlorate, magnesium perchlorate, nitronium perchlorate, and as perchloric acid. As an anion, there is no single Chemical Abstracts Service Registry Number (CASRN) for perchlorate, as each salt has its own properties. Registry numbers for the most common forms of perchlorate and their chemical and physical properties are presented in [REF _Ref353686474 * MERGEFORMAT].

Exhibit [SEQ Exhibit * ARABIC]: Physical and Chemical Properties

Property	Data			
	Perchlorate	Ammonium perchlorate	Potassium perchlorate	Sodium perchlorate
CASRN	14797-73-0	7790-98-9	7778-74-7	7601-89-0
Chemical Formula	$ClO4^-$	NH_4ClO_4	$KClO_4$	$NaClO_4$
Molecular Weight	99.45 g/mol (ChemIDPlus, 2011)	117.49 g/mol (Merck, 1983)	138.55 g/mol (Merck, 1983)	122.44 g/mol (Merck, 1983)

Property	Data			
	Perchlorate	**Ammonium perchlorate**	**Potassium perchlorate**	**Sodium perchlorate**
Color/ Physical State	--	Colorless or white orthorhombic crystals (Hazardous Substances Data Bank [HSDB], 2011)	Colorless orthorhombic crystals or white crystalline powder (HSDB, 2011; Agency for Toxic Substances and Disease Registry [ATSDR], 2008; Merck, 1983)	White orthorhombic, deliquescent crystals (HSDB, 2011; CRC Press, 1981; Merck, 1983)
Boiling Point	--	--	400 deg C dec. (CRC Press, 1981)	--
Melting Point	--	130 deg C (ATSDR, 2008)	400 deg C dec. (ATSDR, 2008); 525 deg C (HSDB, 2011)	471 deg C dec. (ATSDR, 2008) 482 deg C dec (CRC Press 1981); 480 deg C dec. (HSDB, 2011)
Density	--	1.95 g/mL (CRC Press, 1981; Merck, 1983)	2.52 g/mL at 10 deg C (CRC Press, 1981; Merck, 1983)	2.52 g/cm3 (HSDB, 2011); 2.02 g/mL (Merck, 1983; ATSDR, 2008)
Vapor Pressure	--	Very low (ATSDR, 2008)	Very low (ATSDR, 2008)	Very low (ATSDR, 2008)
Solubility in Water	--	200 g/L at 25 deg C (HSDB, 2011); 249 g/L at 25 deg C (ATSDR, 2008)	20.6 g/L at 25 deg C (ATSDR, 2008); 15 g/L at 25 deg C (HSDB, 2011)	2100 g/L at 25 deg C (HSDB, 2011; ATSDR, 2008)
Other Solvents	--	Acetic acid, slightly soluble alcohol (CRC Press, 1981); methanol, slightly soluble ethanol and acetone, very slightly soluble ethyl acetate and ether (HSDB, 2011)	Very slightly soluble alcohol (CRC Press, 1981); insoluble in alcohol and ether (HSDB, 2011)	Alcohol (CRC Press, 1981)

g/mol = grams per mole; "--" indicates that no information was found; deg C = degrees Celsius; dec. = decomposes; g/mL = grams per milliliter; g/cm^3 = grams per cubic centimeter; g/L = grams per liter

2.2 Sources of Perchlorate

Perchlorate is both a naturally occurring and man-made chemical. The following section presents information on perchlorate's natural sources; its production and anthropogenic sources; and environmental fate and transport when naturally occurring or man-made perchlorate is present in soil and/or water.

2.2.1 Natural Sources

Caliche ores, found in Chile, rich in sodium nitrate ($NaNO_3$), are a natural source of perchlorate (USEPA, 2001a). This sodium nitrate (known as Chilean saltpeter) has been mined and refined to produce commercial fertilizers used in the United States. Perchlorate has also been found in other geologic materials. Orris *et al.* (2003) measured perchlorate at levels exceeding 1,000 parts per million (ppm or mg/kg) in several samples of natural minerals, including potash ore from New Mexico and Saskatchewan, Canada; playa crust from Bolivia; and hanksite from California.

Rao *et al.* (2007) found widespread, naturally-occurring perchlorate in diverse unsaturated zones (just below the root zone) in arid and semi-arid regions of Nevada, New Mexico, Texas and Utah. It was postulated that the amount of naturally-occurring perchlorate in aggregate is sufficiently large to affect groundwater when recharge percolates through these unsaturated zones. The perchlorates and other salts (e.g., chlorides) in this region are present due to atmospheric deposition and concentration through evaporation over thousands of years. Walvoord *et al.* (2003) as cited in Trumpolt *et al.* (2005) presents the theory that chlorides from land and sea are blown into the atmosphere where they react photochemically with ozone to produce perchlorate in a process similar to that which produces nitrate. Plummer *et al.* (2005) as cited in Rao *et al.* (2007) cite meteoric events as potential natural sources of perchlorate.

Dasgupta *et al.* (2005) detected perchlorate in many rain and snow samples and demonstrated that perchlorate is formed by a variety of simulated atmospheric processes suggesting that natural, atmospherically derived perchlorate exists in the environment. Barron *et al.* (2006) developed a method for the rapid determination of perchlorate in rainwater samples, with a detection limit (DL) between 70 and 80 ng/L. Of 10 rainwater samples collected in Ireland in 2005, perchlorate was detected in 4 samples at concentrations between 0.075 µg/L and 0.113 µg/L, and in 1 other sample at 2.8 µg/L. Kang *et al.* (2006) conducted seven-day experiments to determine if it was possible to produce perchlorate by exposing various chlorine intermediates to UV radiation in the form of high intensity UV lamps and/or ambient solar radiation. Perchlorate formation was demonstrated in aqueous salt solutions with initial concentrations of hypochlorite, chlorite, or chlorate between 100 and 10,000 mg/L.

2.2.2 Production and Use

While perchlorate has a wide variety of industrial uses, it is primarily used in the form of ammonium perchlorate as an oxidizer in solid fuels used to power rockets, missiles, and fireworks. Perchlorate can also be present in road flares, lubricating oils, matches, aluminum refining, rubber manufacturing, paint and enamel manufacturing, leather tanning, and as a dye mordant.

As noted above, Chilean saltpeter has been mined and refined to produce commercial fertilizers. Before 2001, these accounted for about 0.14% of fertilizer application in the United States (USEPA, 2001a). USEPA (2001a) conducted a broad survey of fertilizers and other raw materials and found that all products surveyed were devoid of perchlorate except for those known to contain or to be derived from mined Chilean saltpeter.

Historically, American Pacific Corporation and Kerr-McGee were the major producers of ammonium perchlorate. Their perchlorate production took place at facilities in Nevada and Utah. Smaller manufacturers located in New York, Oregon, Mississippi, and California ceased production between 1948 and 1975. Kerr-McGee ceased ammonium perchlorate production in July 1998 (Nevada Division of Environmental Protection [NDEP], 2011).

No production data on this contaminant are available from EPA's Inventory Update Reporting program, and no industrial release data are available from EPA's Toxics Release Inventory (TRI). The list of chemicals for which TRI reporting is required has never included perchlorate (USEPA, 2011b).

The Agency for Toxic Substances and Disease Registry (ATSDR) (2008) reports that recent production data for ammonium perchlorate as well as the other forms of perchlorate listed in [REF _Ref353686474 * MERGEFORMAT] are lacking. In 1994, U.S. production of ammonium perchlorate was estimated at 22 million pounds (Mendiratta *et al.,* 1996).

Sodium hypochlorite (NaOCl) is effectively used for water disinfection. However, perchlorate has been detected in hypochlorite solutions. A study by the American Water Works Association and Water Research Foundation (AWWA/WaterRF, 2009) found that perchlorate can be present in hypochlorite solutions and can continue to form with the rate of formation depending on storage conditions. The study found that to minimize perchlorate formation sodium hypochlorite should be stored in dark and cool conditions, diluted if possible, and used within a few weeks of manufacture.

In an earlier limited study, the Massachusetts Department of Environmental Protection (MassDEP) found that perchlorate may be present in sodium hypochlorite solutions used in water and wastewater treatment plants, and that the level of perchlorate occurrence depends upon storage conditions and the initial purity of the stock solution (MassDEP, 2006a). The Town of Tewksbury, Massachusetts conducted a small study to evaluate the impact of storage conditions (temperature and light) on a new shipment of sodium hypochlorite stock solution. Perchlorate concentrations in the new stock solution were found to increase from 0.2 µg/L to levels ranging from 995 µg/L to 6,750 µg/L, depending on the storage conditions. Accounting for the large dilution factor (e.g., 20,000 to 1 ratio) used in chlorination processes at drinking water treatment plants, MassDEP (2006a) concluded that "absent additional efforts to minimize breakdown of hypochlorite solutions, it would appear that low levels of the perchlorate ion (0.2 µg/L to 0.4 µg/L) detected in a drinking water supply disinfected with sodium hypochlorite solutions could be attributable to the chlorination process."

It is not clear at this time what proportion of perchlorate found in public water supplies or entering the food chain comes from these various natural and anthropogenic sources. The significance of different sources likely varies regionally. A study by Dasgupta *et al.* (2006) analyzes the three principal sources of perchlorate and their relative contributions to the food chain. These include use as an oxidizer including rocket propellants, Chilean saltpeter used principally as fertilizer, and perchlorate produced by natural atmospheric processes. Dasgupta *et al.* (2006) concluded that while there may be some localized exceptions, fertilizer with Chilean saltpeter likely has an equal or greater contribution to the food chain than oxidizer contributions

(not including fireworks). Contributions of perchlorate by natural processes are generally even less.

2.3 Environmental Fate and Transport of the Perchlorate Ion

Perchlorate salts are highly soluble in water, and because perchlorate sorbs poorly to mineral surfaces and organic material, perchlorate is mobile in soil and aqueous environments (ATSDR, 2008; USEPA, 2002).

Most perchlorate salts exposed to water will readily dissolve and dissociate into the cation and perchlorate anion (Gullick *et al.*, 2001). The perchlorate ion is unlikely to form insoluble metal complexes in water or be removed from water in this manner (Cotton and Wilkinson, 1980). The perchlorate ion is very stable and inert to reduction despite the high oxidation state of chlorine (Urbansky, 2000). Ionized salts will not undergo hydrolysis and perchlorates are not expected to undergo direct photolysis or to volatilize in water (ATSDR, 2008; HSDB, 2011). Therefore, the ion may persist for decades under normal environmental conditions in ground water and surface water (Gullick *et al.*, 2001).

Biological removal and uptake of perchlorate has been observed in aquatic conditions. Anaerobic microbial biodegradation of perchlorate occurs in anoxic ground water and sediments (ATSDR, 2008). In the absence of nitrate and with influent perchlorate concentrations of up to 32 mg/L, wetlands have been shown to reduce perchlorate concentrations to less than 4 µg/L (Tan *et al.*, 2004). In a study of willow trees in sand bioreactors designed to remove perchlorate from contaminated water, 11% of the original perchlorate concentration measured throughout the whole tree was lost to degradation (to chloride) in the leaves (Nzengung *et al.*, 1999). Aquatic organisms have also demonstrated uptake of perchlorate. One lake study found an indication of food transfer of perchlorate from ingestion of contaminated periphyton, detritus, or invertebrates (Theodorakis *et al.*, 2006). However, another study found that, in aquatic organisms, bioconcentration of perchlorates is low (Dean *et al.*, 2004). For a detailed discussion on the biological treatment of perchlorate see EPA's report entitled, "Technologies and Costs for Treating Perchlorate-Contaminated Waters."

The perchlorate ion is unlikely to adsorb to soil since studies show that in solutions of moderate ionic strength, the perchlorate ion is only weakly adsorbed to mineral surfaces (Logan, 2001; Urbansky and Brown, 2003; Urbansky and Collette, 2001). Therefore, perchlorate will be highly mobile in soil, traveling over the soil with surface water runoff or migrating through the soil to ground water systems (ATSDR, 2008; Gullick *et al.*, 2001). This has been corroborated by studies that have measured perchlorate in surface water and ground water far from release sites (ATSDR, 2008). While perchlorate is not subject to volatilization (partitioning to the gaseous or vapor phase) to any significant extent, it may be transported to the atmosphere by mechanical means: e.g., wind-borne erosion of perchlorate aerosols (fine particles in the solid phase) and perchlorate-contaminated soil particles (ATSDR, 2008).

Removal of perchlorate from the soil by living organisms has been shown to occur through microbial degradation as well as plant uptake and degradation (ATSDR, 2008; Tipton *et al.*, 2003). Anaerobic microbial degradation in soil has been seen in both laboratory and in situ studies; however, soil type and the presence of nitrate will influence the rate of degradation

(Herman and Frankenberger, 1998; Logan, 1998; Tan *et al.*, 2004). In one experimental study, perchlorate in Yolo loam fully degraded in 30 days while no degradation occurred in Columbia loam (Tipton *et al.*, 2003). Both soil samples were three years old. The authors inferred that carbon-rich Yolo loam had preserved colonies of perchlorate-digesting bacteria better than the carbon-poor Columbia loam, and viewed their results as confirming the importance of biodegradation (and the relative unimportance of adsorption) as a fate process for perchlorate in soil. A study of sediment and soil from two Texas sites contaminated by perchlorate showed that degradation in the soil and sediments did not readily occur until most of the nitrate had degraded (Tan *et al.*, 2004). A study of perchlorate uptake by tobacco showed that through a wide range of soil perchlorate concentrations, uptake and accumulation occurred but there were not enough data available to show whether or not the plant degraded the perchlorate (Ellington *et al.*, 2001). Perchlorate uptake in plants has also been observed in salt cedar, cucumber, lettuce, and soybean, though nutrients such as nitrate may hinder the uptake of perchlorate (Urbansky *et al.*, 2000; Yu *et al.*, 2004).

Perchlorate salts released to the atmosphere are expected to exist adsorbed to particulate matter or as solid aerosols (ATSDR, 2008). Removal is likely to occur through deposition not degradation since reaction with gas-phase oxidants and photolysis is unlikely (ATSDR, 2008). A study investigating perchloric acid photolysis in the atmosphere found photolysis to be negligible (Jaegle *et al.*, 1996).

3 Perchlorate Occurrence Data in Unregulated Contaminant Monitoring Rule 1

This section describes the UCMR 1 perchlorate occurrence data set used by EPA to generate national estimates of perchlorate occurrence in drinking water. The agency determined that the best available source of perchlorate occurrence data in drinking water is the EPA administered UCMR 1. UCMR 1 is the only nationally representative drinking water monitoring program that has sampled for perchlorate. This section provides an overview of the UCMR program and the first UCMR monitoring cycle, UCMR 1. Details are provided to characterize the UCMR 1 data including sampling schedule, frequency, locations, system source water types and size, and the perchlorate laboratory analytical method used. See Section 4 for a more detailed discussion of the perchlorate occurrence analysis conducted using the UCMR 1 data.

In addition to the UCMR 1 data, EPA evaluated numerous national-scale studies and surveys, and state-sponsored studies of perchlorate occurrence in drinking water and ambient water. Appendix A presents a summary of these datasets, with the exception of the State of California. Data from the State of California are described separately and in detail in Appendix B.

3.1 UCMR 1 Program Overview

In 1999, EPA developed the UCMR program in coordination with the Contaminant Candidate List (CCL) and the National Drinking Water Contaminant Occurrence Database to provide national occurrence information on unregulated contaminants (64 FR 50556, USEPA, 1999d; 65 FR 11372, USEPA, 2000; and 66 FR 2273, USEPA, 2001b). UCMR 1 established a three-tiered approach for monitoring contaminants based on the availability of analytical methods and information on contaminant properties. The first tier and highest priority of the three-tier ranking system, designated as List 1, included perchlorate and other unregulated contaminants for which suitable laboratory methods are available; these were scheduled to undergo full "Assessment Monitoring."

The UCMR operates on a five-year cycle, with the first cycle extending from 2001 through 2005, although most monitoring was conducted from 2001 to 2003. For UCMR 1, EPA required all PWSs serving more than 10,000 people ("large" systems), plus a statistically representative national sample of 800 PWSs serving 10,000 people or fewer ("small" systems), to conduct Assessment Monitoring of List 1 contaminants (USEPA, 2001c). Approximately one-third of the participating small systems were scheduled to monitor List 1 contaminants during each calendar year from 2001 through 2003. Large systems could conduct one year of monitoring for List 1 contaminants anytime during the 2001-2003 UCMR 1 period.

The UCMR 1 program design, including system selection and overall monitoring approach, was peer reviewed (USEPA, 1999e). The program was designed expressly to provide nationally representative occurrence data for unregulated contaminants in public drinking water

systems.[6] There is no nationally representative alternative to the UCMR 1 data. EPA selected PWSs to conduct monitoring for the UCMR 1 program based on the number of people they serve, the source of their water, and whether they serve the same customers year-round. All large community water systems (CWSs) and non-transient non-community water systems (NTNCWSs), as well as a national sample of 800 small CWSs and NTNCWSs were required to conduct monitoring under the UCMR 1. Two categories of PWSs were exempt from UCMR 1 monitoring: PWSs that purchase their entire water supply from another PWS and transient non-community water systems (TNCWSs). For more details on the classification of public drinking water systems, go to: [HYPERLINK "http://water.epa.gov/infrastructure/drinkingwater/pws/factoids.cfm"].

The objective of the UCMR 1 sampling approach for small systems was to collect contaminant occurrence data from a statistically selected, nationally representative sample of systems. Small system sampling was stratified and population-weighted, and included some sampling adjustments such as selection of at least two systems from each state. As previously stated, with contaminant monitoring data from all large PWSs and a nationally representative sample of small PWSs, the UCMR 1, List 1 Assessment Monitoring program is nationally representative of contaminant occurrence in public drinking water systems and therefore is suitable for national estimates of perchlorate occurrence in public drinking water systems.

Perchlorate occurrence is known to have decreased in some important source waters (such as the Lower Colorado River) and in the two states (Massachusetts and California) that now regulate perchlorate in drinking water. (These important cases are discussed in Appendix A and Appendix B of this report.) However, because perchlorate remains unregulated and largely unmonitored across most of the United States, other locations, areas and regions have no newer comparable data (and across these other regions perchlorate occurrence could have stayed about the same, increased or decreased). Therefore, to conduct a consistent and statistically sound assessment of national perchlorate occurrence in public drinking water systems, EPA is using a modified UCMR 1 dataset in this report.

3.2 Monitoring Frequency and Location

UCMR 1 required surface water systems to sample four times at each entry point to the distribution system (or entry point) over a one-year period, while ground water systems were required to sample twice per entry point over a one-year period. One of the quarterly (surface water systems) or semi-annual (ground water systems) sampling events had to occur in the defined vulnerable[7] period of May through July, or an alternate vulnerable period designated by the state, to ensure monitoring of potentially higher contaminant concentrations. Surface water systems had to select either the first, second, or third month of a quarter and then take the remaining samples at three-month intervals for the following three quarters of the monitoring year. Ground water systems were required to designate a sample collection during one of the

[6] See USEPA (2005e), USEPA (2007b), and USEPA (2008b) for more information on all aspects of UCMR 1, including study design, completeness, and quality assurance/quality control procedures.

[7] For UCMR 1 a vulnerable period is the season of greatest likelihood of contaminant occurrence, generally the months of late spring and early summer which are characterized by high volumes of surface water runoff and ground water recharge.

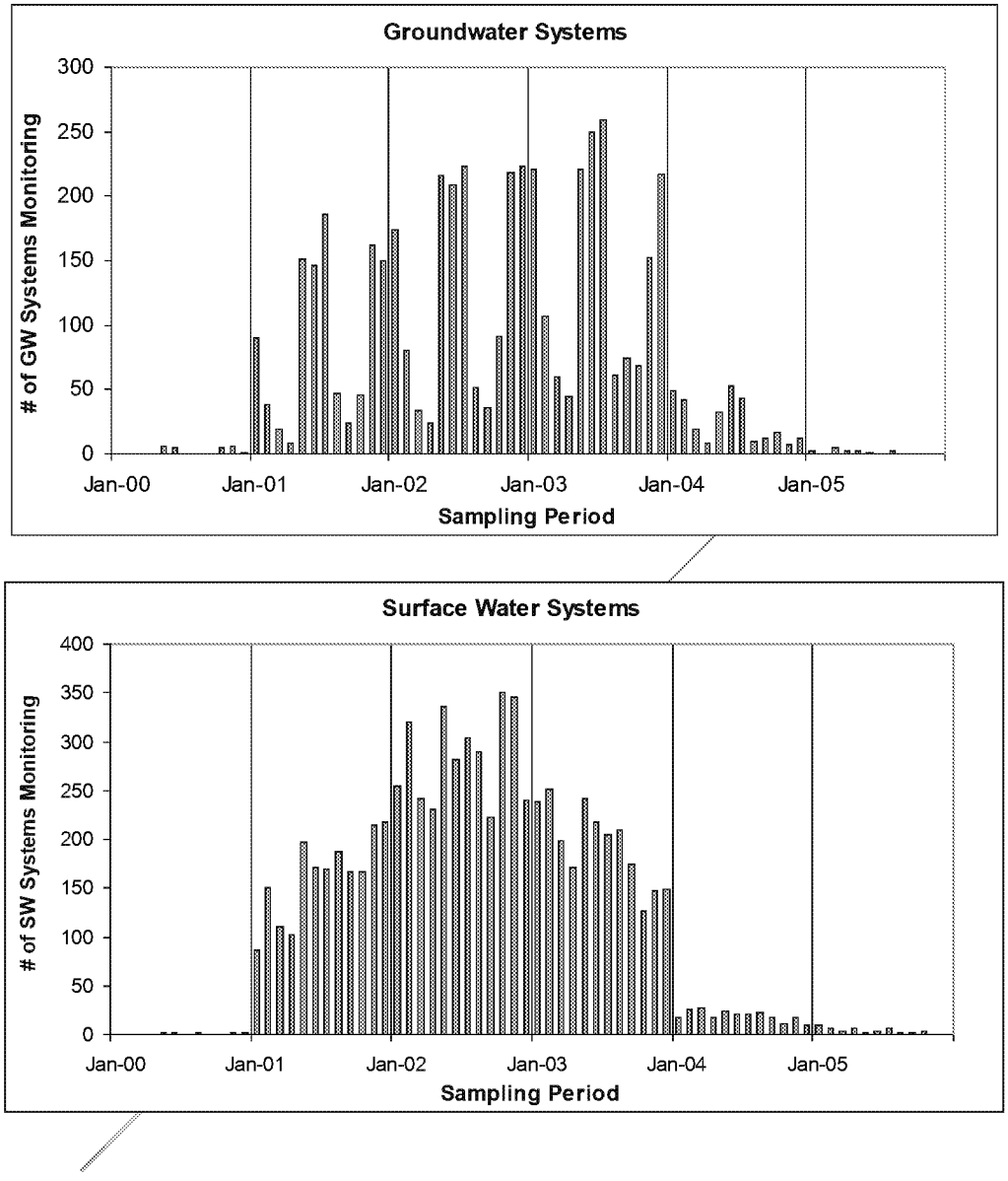
most vulnerable months, and then schedule another sample collection within five to seven months.

PWSs sampled at entry points after treatment. These entry points were meant to be representative of each principal non-emergency source of water in use over the 12-month monitoring period. UCMR 1 explicitly allowed source water monitoring, under certain conditions. As EPA stated in the Federal Register on September 17, 1999, "In response to public comment, EPA modified the rule [from the proposal] to allow alternative sampling points to be used: sampling points identified by the State for compliance monitoring under 40 CFR 141.24(f)(1), (2), and (3), and/or source (raw) water sampling points, if the State uses source water monitoring as a more stringent monitoring requirement" (64 FR 50570; USEPA, 1999d). EPA also stated that, "If monitoring at source (raw) water sampling points indicates detection of any of the contaminants on the monitoring list, then the system in most cases will be required to shift its unregulated contaminant monitoring to the entry point to the distribution system. These flexibilities in the sampling location should enable systems and States to coordinate compliance and unregulated contaminant monitoring more extensively."

EPA designed the UCMR 1 program with geographic, geologic, and temporal variability in mind. A census of all large systems and a primarily population-weighted statistical sample of small systems ensured monitoring across the varied geography and geology of the country. An additional program requirement was the selection for monitoring of at least two small systems in each state. The study design addressed temporal variability in contaminant occurrence by defining a vulnerable period and requiring at least one UCMR 1 sample at each system during that period. Large systems could conduct their one year of monitoring anytime during the UCMR 1 period from 2001 to 2003. Like small systems, their monitoring schedules were spread throughout the year and were to include one sample during what was considered the most vulnerable season. In this way, the national UCMR 1 results reflect multiple seasons and multiple years across the country and therefore are not biased by weather conditions of a single season, year, or geographic region.

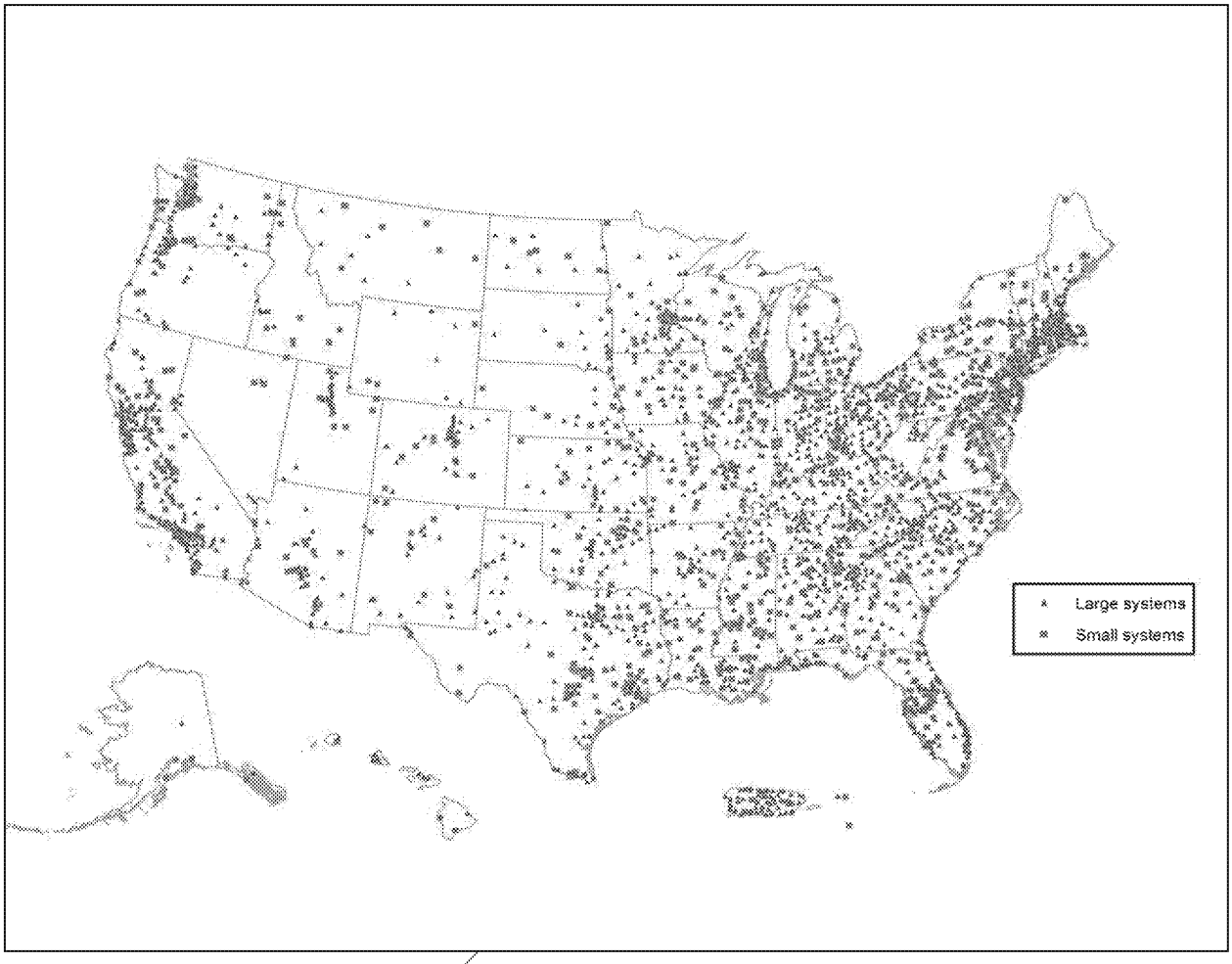
[REF _Ref526571210 \h] illustrates the monthly distribution of ground water and surface water perchlorate sampling events. Ground water sampling events, which were conducted biennially, were concentrated in the summer months (May, June, July) and the winter months (November, December, January). No distinct seasonal pattern is evident in the surface water sampling, as those systems sampled on a quarterly schedule.

Exhibit [SEQ Exhibit * ARABIC]: Number of PWSs Collecting UCMR 1 Ground Water (GW) and Surface Water (SW) Samples for Perchlorate Analysis by Month During the Sampling Period (Top: GW Systems; Bottom: SW Systems)



[REF _Ref358310547] is a map of all large and small systems that submitted UCMR 1 data to EPA. At least two small systems were sampled in every state and most territories. One large system and two small systems from American Samoa were originally included in the sampling plan, but none of these three systems provided data.

Exhibit [SEQ Exhibit * ARABIC]: PWSs with UCMR 1 Monitoring Results



3.3 Completeness of UCMR 1 Perchlorate Dataset

To ensure that occurrence estimates based on UCMR 1 data dependably reflect national conditions, EPA assessed the completeness and representativeness of the UCMR 1 contaminant sample data. Background discussions of data quality issues can be found in the UCMR 1 statistical design (USEPA, 2001d) and the quality assurance project plan (QAPP) (USEPA, 2003). The QAPP specified quantitative data quality objectives (DQOs) for the completeness and representativeness of small system data collected under UCMR 1. The small system data in the final UCMR 1 data set satisfy those DQOs, indicating the small system data are complete and representative. Although no formal DQOs were established for large systems, the large system census had a very high participation rate and a very large portion of the submitted data passed the general data quality criteria checks. These and other quality assessments suggest the large system contaminant occurrence data are dependable for national contaminant occurrence analyses.

Nearly all PWSs (99.2%) reported the results of their perchlorate assessment results to EPA (3,865 large and small PWSs responded out of a total of 3,897 PWSs). Of the 800 representative small systems required to collect samples, EPA received monitoring results from 797 systems (99.6%). Of the 3,097 large systems identified for inclusion in the census, EPA received monitoring results from 3,068 systems (99.1%). About two-thirds of the non-responsive systems were served by ground water (note that perchlorate detections were more frequent in surface water systems).

Texas had 37.5% (12 of the 32) of the non-responsive large PWSs. Of the 184 large PWSs in Texas that did report perchlorate results, about 2.2% had perchlorate detections. (Nationally, an estimated 4.6% of large PWSs reported at least one detection of perchlorate). These 32 non-responsive large systems serve approximately 0.7% of the total population. If any of these non-responsive systems had detectable levels of perchlorate, then the UCMR 1 results would underestimate actual occurrence.

3.4 Summary of UCMR 1 Perchlorate Monitoring Data and QA/QC Review

This section provides a description of the two phases of QA/QC review of the UCMR 1 Perchlorate Dataset. Section 3.4.1 describes EPA's initial quality review and data check of the UCMR 1 data. Section 3.4.2 describes EPA's consideration of the "Information Quality Guidelines (IQG) Request for Correction" received from the Chamber of Commerce in September 2012 and the resulting QA/QC review of the UCMR 1 perchlorate data. Section 3.4.3 summarizes the final version of the UCMR 1 perchlorate data set (post-QA/QC reviews) that was used as the basis of the occurrence analyses presented in this report.

3.4.1 QA/QC Review – Phase 1

UCMR 1 data were collected from all 50 states, plus Washington, D.C., Tribal Nations, Puerto Rico, the American Virgin Islands, Guam, and the Commonwealth of the Northern Mariana Islands. A total of 34,728 perchlorate samples were collected with 647 detections reported. Samples were collected between May 1, 2000 and October 25, 2005, with almost 94% of samples collected between January 2001 and December 2003. EPA reviewed the 34,728 perchlorate samples and identified 397 sample records (10 of which were detections) that did not meet quality approval requirements for the following reasons:

(1) records from non-approved perchlorate labs;

(2) records identified as duplicates (i.e., having the same PWSID, Facility ID, Sample Point ID, and sample collection date)
   a. if there were duplicate detections, the lesser of the two analytical results was deleted;
   b. if there was a mix of non-detect and detect duplicates, the non-detect record was deleted;
   c. if there were duplicate non-detections, all but one of the duplicate records was deleted;

(3) records from CA4810015 were deleted because it was determined the system uses the same water source as CA4810003, and including data from both systems would provide duplicate results; and

(4) records from four systems were excluded (MA4261024, PR0005226, PR0005246, and PR0005617) because the size of the populations they served had changed and they were no longer officially considered large systems.

In all, 397 samples and 10 detections were identified from the QA/QC review described above; see USEPA (2008b) for more information on the QA/QC review. Excluding those 397 samples and 10 detections resulted in a UCMR 1 perchlorate data set with 34,331 samples from 3,865 PWSs with a reported 637 detections. A second phase of data quality checks, described below in Section 3.4.2, resulted in additional revisions to the data set.

3.4.2 QA/QC Review – Phase 2

In September of 2012, EPA received a "Request for Correction" letter from the United States Chamber of Commerce regarding information and data (regarding the occurrence of perchlorate in drinking water) used by EPA in its determination to regulate perchlorate. This letter stated that EPA relied upon data that did not comply with data quality guidelines. In response to the letter, EPA reassessed some components of the UCMR 1 data and some more recent studies that considered local perchlorate occurrence. A summary of EPA's consideration of the Chamber of Commerce comments is included below. Additional details regarding these considerations are included in Appendix C of this report.

UCMR 1 Perchlorate Source Water Sampling Data Review

The Chamber of Commerce letter stated that some UCMR 1 raw source water sample analytical detections of perchlorate did "not comply with data quality guidelines because it was not collected by accepted methods." Of the 34,331 total samples in the UCMR 1 Perchlorate Dataset, 69% (23,731) were collected at the entry points to the distribution system while the remaining 31% (10,600) were collected from untreated (but UCMR 1 eligible) source water sample locations. Of the 637 samples that detected perchlorate, 56% (355) were collected at the entry points to the distribution system while the remaining 44% (282) were collected from source water sample locations. All source water samples with perchlorate detections were collected from PWSs serving more than 10,000 people.

In a response to the Chamber of Commerce in February of 2013,[8] EPA explained that UCMR 1 allowed source water sampling points in a particular State if that State uses source water monitoring as a more stringent compliance monitoring requirement. EPA did, however, conduct a more detailed assessment of the source water sample detections; a detailed description of this evaluation is presented in Appendix C. Ultimately, EPA determined that, as is consistent with State compliance monitoring programs that enable source water sampling, it was most appropriate to exclude the source water sample detections from the UCMR 1 Perchlorate Dataset

[8] [HYPERLINK "https://www.epa.gov/sites/production/files/2015-06/documents/12004-response.pdf"]

when those samples had appropriate follow-up entry point samples that were included in the UCMR 1 Perchlorate Dataset. In contrast, any source water sample perchlorate detections for which no follow-up entry point sampling was conducted by PWSs were retained in the UCMR 1 Perchlorate Dataset. Following this convention, the resulting UCMR 1 data set contains 34,132 perchlorate samples from 3,865 systems with a total of 540 detections[9] (1.58% of all samples) from 149 PWSs (3.86% of all PWSs).

Follow-up Information Relevant to UCMR 1 Perchlorate Data

The Chamber of Commerce letter also stated that some UCMR 1 data did "not comply with data quality guidelines because it is not representative of current conditions." The Chamber of Commerce provided information on follow-up sampling, as well as additional research into some of the UCMR 1 perchlorate sampling and detections that indicated some of the detections included in the UCMR 1 data set did not fully reflect conditions at some PWSs at the time of the UCMR 1 sampling. Information such as state drinking water annual compliance reports, and studies by Brandhuber *et al.* (2009) and AWWA (2008) were noted by the Chamber and were reviewed and considered by EPA.

In response to the Chamber's request, the EPA evaluated publicly available compliance data from the States of California and Massachusetts. The UCMR 1 dataset was designed to be nationally representative of perchlorate occurrence at the time of sampling (2001 through 2005). EPA acknowledges that conditions may have changed regarding perchlorate occurrence after the time of UCMR 1 sampling. EPA believes that it is important to consider the effect that the State mandated regulations for perchlorate in drinking water has had on the contaminant occurrence in public water systems.

To update the occurrence data for systems sampled during UCMR1 from the States of California and Massachusetts, EPA identified all systems and corresponding entry points which had reported perchlorate detections in UCMR 1. Once the systems and entry points with detections were appropriately identified, EPA then used a combination of available data from Consumer Confidence Reports (CCRs) and perchlorate compliance monitoring data from California ([HYPERLINK "https://sdwis.waterboards.ca.gov/PDWW/"]) and Massachusetts ([HYPERLINK "https://www.mass.gov/service-details/public-water-supplier-document-search"]) to match current compliance monitoring data (where available) to the corresponding water systems and entry points sampled during UCMR1.

Out of the 540 detections resulting from the previous QA/QC step, EPA updated data for 321 detections (320 from California systems & 1 from a Massachusetts system). The convention used by EPA to accomplish the substitution of data was to match entry points with compliance data for active entry points based on most recently reported monitoring compliance data, if more than one data point was reported for an entry point, the assigned value is an average of the annual monitoring results at the entry point. In cases were EPA could not find updated entry point data, then the original data from UCMR1 for such entry point was kept.

[9] The 540 detections are the result of the original 637 detections in the UCMR 1 minus 97 source water detections.

In addition, EPA used CCRs information for its data update effort. The process for data substitution using CCR information was accomplished by assigning a default value of 6 ppb to all entry points in a given system if perchlorate was reported in the CCR as detected and within compliance of the California MCL. For other systems, if perchlorate was reported as not detected in the CCR then a default value of 4 ppb (equal to the MRL) was assigned to all entry points in a given system. Appendix C includes copies of the State compliance records utilized by EPA for the data substitution effort.

3.4.3 UCMR 1 Perchlorate Data Subsequent to Phase 1 and 2 QA/QC Review

Subsequent to the two phases of QA/QC review of the UCMR 1 perchlorate data, a total of 34,132 samples from 3,865 systems remained, including a total of 540 detections. This data set, referred to as the "UCMR 1 Perchlorate Dataset (2018 Version)," serves as the basis for all occurrence analyses, graphs, and maps presented in Section 4 of this report. [REF _Ref526856259 \h] summarizes the count of records removed from the two phases of QA/QC review.

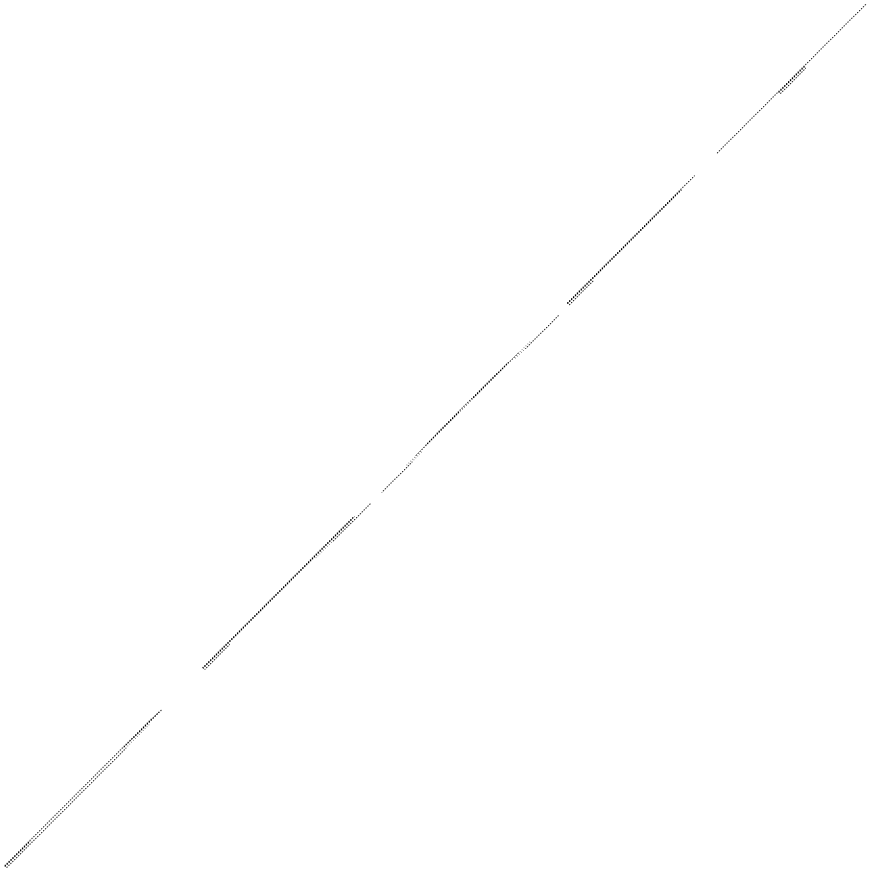
Exhibit [SEQ Exhibit * ARABIC]: Counts of the Number of Records Removed from the UCMR 1 Perchlorate Data set from Phase 1 and Phase 2 of QA/QC Review

Step	UCMR 1 Perchlorate Data	
	Included	Excluded
Original Records	34,728	
Phase 1: Removal of duplicates, data from non-approved perchlorate labs, and data from systems no longer considered large systems. See Section 3.4.1 for details.	34,331	397
Phase 2: Removal of source water detections that had follow-up entry point samples that were included in the UCMR 1 Perchlorate Dataset. See Section 3.4.2 and Appendix C for details.	34,132	199
Final Records	34,132	
Percent Included	98.3%	

Note that Appendix D presents all 637 perchlorate detections from UCMR 1 sampling included in the data set prior to the Phase 2 QA/QC review (i.e., removal of source water detections with follow-up entry point sample). Specifically, the table in Appendix D presents (for each of the 637 original UCMR 1 individual detections) the state, public water system identification number (PWSID), Facility ID, sample point ID, sample point type (EP = entry point; SR = source water), the system's source water type, system size, the sample date, the result value (in µg/L), and the source water sample category (if the detection was from source water).

3.5 UCMR 1 Analytical Method 314.0

EPA developed Method 314.0, revision 1.0 for the analysis of perchlorate under the UCMR 1. The Minimum Reporting Level (MRL) was 4 µg/L and was based on EPA's experience and detailed assessments during method development. The ability to reliably quantify a concentration less than 4 µg/L was not evaluated at the time because this MRL was adequate given the general levels of health concern during development of the UCMR 1 in the late 1990s. This analytical method was the only method used to analyze UCMR 1 water samples for perchlorate analysis. All perchlorate laboratory analytical results generated under UCMR 1 have undergone QA/QC review according to the UCMR 1 program. For a detailed discussion of laboratory analytical methods for perchlorate see Section 5.



4 Analysis of the UCMR 1 Perchlorate Dataset

EPA has evaluated the available peer-reviewed science, perchlorate occurrence studies, and data collected by accepted methods on the national occurrence of perchlorate in drinking water. EPA has determined that UCMR 1 is the best available nationally representative data on the frequency and degree (concentration) of perchlorate in drinking water. As previously discussed, the UCMR 1 perchlorate monitoring of drinking water – conducted by a census of large PWSs (serving more than 10,000 people) and a nationally representative statistical sample of small systems (serving 10,000 people or fewer) – represents the most extensive, nationally representative monitoring program for perchlorate in public drinking water systems.

Section 4.1 describes the analytical approach used and provides the resulting tabulated and graphical findings that characterize the national occurrence of perchlorate in drinking water, based on the UCMR 1 data. The perchlorate occurrence findings are presented relative to a range of concentration thresholds to enable a characterization of the frequency and degree of perchlorate occurrence. The results of the analysis are presented in Sections 4.2, 4.3, and 4.4.

4.1 Analytical Approach and Resulting Occurrence Estimates

EPA analyzed the updated UCMR 1 perchlorate occurrence data described in Section 3.4.3 above (34,132 samples with 540 detections from 149 systems) to estimate the frequency and degree of perchlorate in public drinking water systems and to estimate the population-served by those systems. To estimate analytical monitoring results, EPA used a non-parametric approach which includes the number and percent of UCMR 1 samples with an analytical detection (a measured sample concentration of perchlorate) that exceeds a concentration threshold of interest. These counts are done at the system level and sample point level to characterize national perchlorate occurrence. Perchlorate occurrence was assessed relative to a range of concentration thresholds including 4 µg/L, 18 µg/L, and 56 µg/L. Additionally, assessments relative to the threshold of greater than or equal to 4 µg/L served to identify all perchlorate sample detections. The results of the analyses are presented in terms of number or percent of PWSs and/or samples with perchlorate concentrations greater than a particular threshold. Additionally, the number and percent of the population served by systems or by sample points with detections is also presented to provide an estimate of the population consuming public drinking water with various frequencies and degrees of perchlorate occurrence.

A limitation of the non-parametric approach is that it can only be used for threshold concentrations that are at or above the UCMR 1 MRL of 4 µg/L for perchlorate. There are also no measures of uncertainty or estimates of error. The national estimates of perchlorate occurrence based on the non-parametric analyses of the UCMR 1 data are found in Sections 4.2.1 and 4.2.2 with additional state-level details presented in Appendix E. [REF _Ref358311810] presents some summary statistics of the UCMR 1 data used for all national occurrence analyses in this section.

Exhibit [SEQ Exhibit * ARABIC]: Perchlorate Detection Rates and Summary of Detected Concentrations Based on the Updated UCMR 1 Perchlorate Dataset

Source water Type	Total Number of Samples	Samples with Detections	Concentration Value of Detections (µg/L)		
			Minimum	Median	Maximum
Small Systems (serving ≤ 10,000 people)					
Ground Water	2,355	6	4.3	5.3	19.6
Surface Water	940	9	4.5	5.9	6.8
All Small Systems	**3,295**	**15**	**4.3**	**5.8**	**19.6**
Large Systems (serving > 10,000 people)					
Ground Water	16,121	166	4	6.1	70
Surface Water	14,716	359	4	6.7	420
All Large Systems	**30,837**	**525**	**4**	**6.6**	**420**
All Systems					
All Systems	**34,132**	**540**	**4**	**6.5**	**420**

As a supplement to the non-parametric occurrence analyses presented in this report, EPA also conducted parametric probabilistic modeling of national occurrence of perchlorate using the UCMR 1 Perchlorate Dataset (June 2013 Version). These model analyses estimate national perchlorate occurrence (including national extrapolations of the sample of small systems) provide projections of occurrence below the MRL of 4 µg/L, and generate estimates of uncertainty and model error.

4.2 System-Level Analyses

EPA analyzed the updated UCMR 1 Perchlorate Dataset to determine system-level occurrence for the number of systems (and population served by those systems) with one or more analytical detections, and the number of systems with two or more analytical detections. EPA also evaluated the number of systems that had at least one detection at two of its sample points. This measure addresses the distribution of perchlorates occurrence throughout a system. For analyses relative to a particular concentration threshold, if a system is identified with two or more detections at a sample point, EPA used the maximum detected concentration in the analysis to estimate potential exposure for the population served by that system.

Perchlorate system-level occurrence analyses are presented in [REF _Ref358312523] through [REF _Ref368308823 \h]. These analyses characterize the frequency and degree of perchlorate occurrence at concentrations (or thresholds) of 4, 18, and 56 µg/L.

[REF _Ref358312523 * MERGEFORMAT] presents the number of PWSs and associated populations that had at least one analytical detection of perchlorate relative to the various thresholds. A total of 149 systems serving approximately 16.2 million people were served water from PWSs that had at least one detection of perchlorate. As the detection threshold increases, the number of affected systems and associated populations decrease. At 18 µg/L, the

number of systems reporting perchlorate detections drops to 15 systems serving approximately 700,000 people. Two systems serving approximately 65,000 people had detections greater than 56 µg/L.

[REF _Ref358312598] presents the number of PWSs and associated populations that had two or more analytical detections of perchlorate relative to the various thresholds. This estimate provides an assessment of perchlorate persistent or recurring occurrence. A total of 73 systems serving approximately 12 million people had two or more detections of perchlorate. As the detection threshold increases, the number of affected systems and associated populations decrease. At 18 µg/L, the number of systems reporting perchlorate detections drops to 1 system serving approximately 40,000 people.

[REF _Ref368308823] presents the number of systems and associated populations that had at least one analytical detection at two or more sample points above the various thresholds. This assessment attempts to address the distribution of perchlorate occurrence throughout a system. Note that roughly half of all UCMR 1 systems sampled only at one sample point and, therefore, were not included in this analysis. A total of 52 systems (all large systems) serving about 10.8 million people had at least one detection of perchlorate at two or more sampling points. As the thresholds increase, the number of systems and associated proportional populations decrease.

Exhibit [SEQ Exhibit * ARABIC]: Systems and Populations with a ***SINGLE*** Detection Relative to Various Thresholds Based on the Updated UCMR 1 Perchlorate Dataset

System Type	Source Water Type	Total Number of Systems in UCMR 1	Total Pop. Served by Systems in UCMR 1	Concentration Thresholds					
				≥ 4 µg/L		> 18 µg/L		> 56 µg/L	
				Number of Systems	Pop. Served	Number of Systems	Pop. Served	Number of Systems	Pop. Served
Small Systems (serving ≤10,000)	Ground Water	590	1,939,815	5	7,360	1	4,309	0	0
	Surface Water	207	820,755	3	6,123	0	0	0	0
	All Systems	**797**	**2,760,570**	**8**	**13,483**	**1**	**4,309**	**0**	**0**
Large Systems (serving >10,000)	Ground Water	1,379	53,765,152	62	4,474,125	6	173,480	1	38,761
	Surface Water	1,689	169,087,949	79	11,684,957	8	523,391	1	25,972
	All Systems	**3,068**	**222,853,101**	**141**	**16,159,082**	**14**	**696,871**	**2**	**64,733**
All Systems	Ground Water	1,969	55,704,967	67	4,481,485	7	177,789	1	38,761
	Surface Water	1,896	169,908,704	82	11,691,080	8	523,391	1	25,972
	All Systems	**3,865**	**225,613,671**	**149**	**16,172,565**	**15**	**701,180**	**2**	**64,733**

Exhibit [SEQ Exhibit * ARABIC]: Systems and Populations with ***TWO OR MORE*** Detections Relative to Various Thresholds Based on the updated UCMR 1 Perchlorate Dataset

System Type	Source Water Type	Total Number of Systems in UCMR 1	Total Pop. Served by Systems in UCMR 1	Concentration Thresholds					
				≥ 4 µg/L		> 18 µg/L		> 56 µg/L	
				Number of Systems	Pop. Served	Number of Systems	Pop. Served	Number of Systems	Pop. Served
Small Systems (serving ≤10,000)	Ground Water	590	1,939,815	1	56	0	0	0	0
	Surface Water	207	820,755	3	6,123	0	0	0	0
	All Systems	**797**	**2,760,570**	**4**	**6,179**	**0**	**0**	**0**	**0**
Large Systems (serving >10,000)	Ground Water	1,379	53,765,152	32	3,105,652	0	0	0	0
	Surface Water	1,689	169,087,949	37	9,044,290	0	0	0	0
	All Systems	**3,068**	**222,853,101**	**69**	**12,149,942**	**0**	**0**	**0**	**0**
All Systems	Ground Water	1,969	55,704,967	33	3,105,708	0	0	0	0
	Surface Water	1,896	169,908,704	40	9,050,413	0	0	0	0
	All Systems	**3,865**	**225,613,671**	**73**	**12,156,121**	**0**	**0**	**0**	**0**

Exhibit [SEQ Exhibit * ARABIC]: Systems and Populations with At Least One Detection At Two or More Sample Points Based on the updated UCMR 1 Perchlorate Dataset

System Type	Source Water Type	Total Number of Systems in UCMR 1	Total Pop. Served by Systems in UCMR 1	Concentration Thresholds					
				≥ 4 µg/L		> 18 µg/L		> 56 µg/L	
				Number of Systems	Pop. Served	Number of Systems	Pop. Served	Number of Systems	Pop. Served
Small Systems (serving ≤10,000)	Ground Water	590	1,939,815	0	0	0	0	0	0
	Surface Water	207	820,755	0	0	0	0	0	0
	All Systems	**797**	**2,760,570**	**0**	**0**	**0**	**0**	**0**	**0**
Large Systems (serving >10,000)	Ground Water	1,379	53,765,152	24	2,890,719	1	38,761	0	0
	Surface Water	1,689	169,087,949	28	7,951,355	0	0	0	0
	All Systems	**3,068**	**222,853,101**	**52**	**10,842,074**	**1**	**38,761**	**0**	**0**
All Systems	Ground Water	1,969	55,704,967	24	2,890,719	1	38,761	0	0
	Surface Water	1,896	169,908,704	28	7,951,355	0	0	0	0
	All Systems	**3,865**	**225,613,671**	**52**	**10,842,074**	**1**	**38,761**	**0**	**0**

4.3 Sample Point-Level Analyses

The system-level analysis in Section 4.2.1, while valuable for illustrative purposes, reflects the conservative assumption that if a perchlorate detection is found in a single entry (or sampling) point in a system, even in a system with multiple entry/sampling points, then the entire population served by the system is potentially served water containing perchlorate. However, there are 2,004 UCMR 1 PWSs that have more than 1 sample point and some get water from multiple water sources (such as a mix of purchased and non-purchased water, ground water and surface water, etc.). In systems with multiple water sources or water intakes, contaminant occurrence in one source or entry point does not necessarily mean occurrence in all sources or entry points that distribute water to consumers. Given the detailed sample point information in the UCMR 1 data, EPA conducted analyses at the sample point level to provide additional details of contaminant occurrence by sample point. These occurrence measures include a sample point "proportional population" occurrence assessment that estimates potential exposure (population served with water containing perchlorate) based on perchlorate occurrence at the sample point (instead of the entire PWS) level. These sample point level analyses were conducted for sample points with at least one perchlorate analytical detection, as well as sample points with two or more perchlorate analytical detections.

Sample Point "Proportional Populations"

The sample point proportional population occurrence measure is a less conservative estimate of the population served by a system with a perchlorate detection. The actual population served by the different distribution systems within a PWS with multiple distribution systems is not known; these data are not required for reporting. Therefore, to derive this sample point-level measure, EPA assumed that all distribution systems at PWSs with multiple distribution systems evenly serve the system's population. For example, if a PWS has two distribution systems, serves a population of 30,000, and has an analytical detection of perchlorate in one of its two sample locations, then a population of 15,000 (one half of 30,000) would be estimated to be potentially exposed to perchlorate. How well this assumption reflects actual populations exposed to perchlorate occurrence depends on the distribution system and service population configurations of individual systems.

Two Detections at One Sample Point

The "two detections at one sample point" occurrence measure identifies which PWSs have at least two or more analytical detections at any single sample point in the system. By counting individual sample points with at least two separate detections, the analysis provides an indication of persistent or recurring perchlorate occurrence over time at the particular sampling point location within the system. For analyses relative to a particular concentration threshold, if a system is identified with two or more detections at a sample point, EPA used the maximum detected concentration in the analysis to estimate potential exposure for the population served by that system.

These occurrence analyses are also presented relative to perchlorate concentrations thresholds of 4, 18, and 56 µg/L. At all thresholds, detection rates were higher in large systems than in small systems.

[REF _Ref358346528] presents the number of sample points in UCMR 1 that had at least one perchlorate detection. A total of 336 sample points serving about 4.1 million people had at least one perchlorate detection. As the perchlorate concentration thresholds increase, the number of sample points and associated proportional populations decrease, ending at the 18 µg/L threshold with 50 sample points, serving about 1.1 million people.

[REF _Ref358313783] presents the number of sample points in UCMR 1 that had at least two perchlorate detections above the perchlorate concentration thresholds. As described earlier, this analysis provides an indication of persistent, or recurring, perchlorate occurrence over time at the particular sampling location within the system. A total of 126 sample points serving about 1.2 million people had at least two detections of perchlorate). As the thresholds increase, the number of systems and associated proportional populations decrease, ending at the 18 µg/L threshold with 11 sample points, serving about 50,700 people.

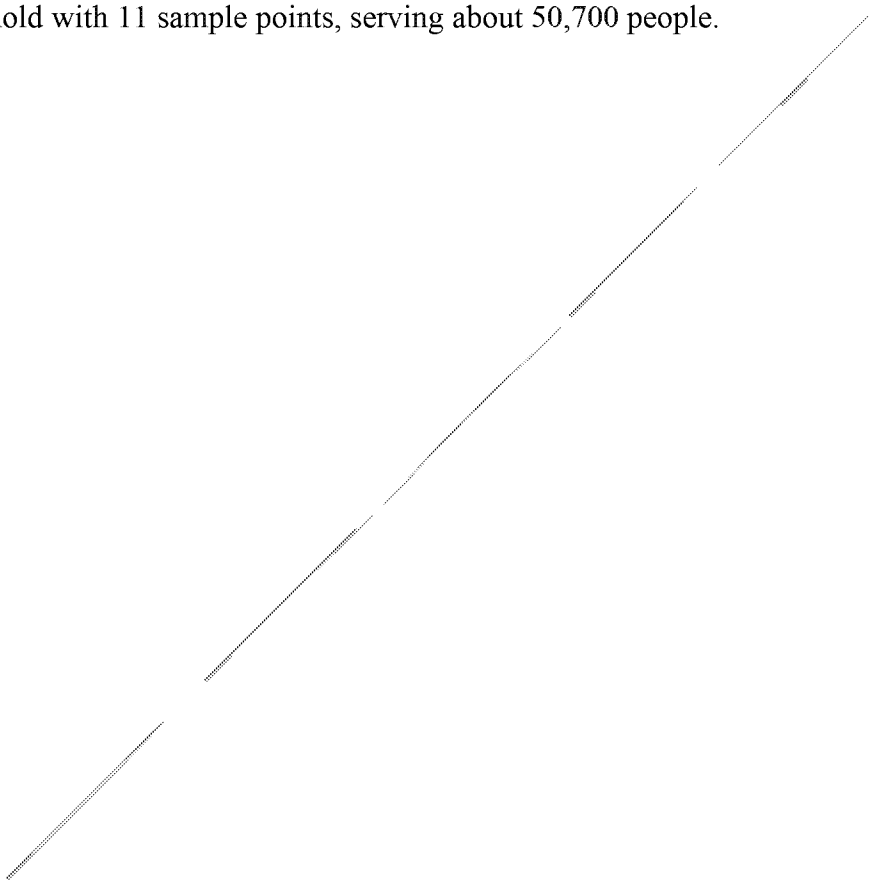


Exhibit [SEQ Exhibit * ARABIC]: Sample Points With at Least One Detection and Their Proportional Populations Based on the UCMR 1 Perchlorate Dataset (June 2013 Version)

System Type	Source Water Type	Total UCMR 1 Sample Points	Total UCMR 1 Population	Concentration Thresholds					
				≥ 4 µg/L		>18 µg/L		>56 µg/L	
				Number of Sample Points	Proportional Population	Number of Sample Points	Proportional Population	Number of Sample Points	Proportional Population
Small Systems (serving ≤10,000)	Ground Water	1,211	1,939,815	5	3,361	5	3,361	1	2,155
	Surface Water	243	820,755	3	6,123	3	6,123	0	0
	All Systems	**1,454**	**2,760,570**	**8**	**9,484**	**8**	**9,484**	**1**	**2,155**
Large Systems (serving >10,000)	Ground Water	8,212	53,765,152	123	628,539	116	591,693	34	242,251
	Surface Water	5,270	169,087,949	205	3,434,702	198	3,373,780	69	1,272,029
	All Systems	**13,482**	**222,853,101**	**328**	**4,063,241**	**314**	**3,965,473**	**103**	**1,514,280**
All Systems	Ground Water	9,423	55,704,967	128	631,900	121	595,054	35	244,406
	Surface Water	5,513	169,908,704	208	3,440,825	201	3,379,903	69	1,272,029
	All Systems	**14,936**	**225,613,671**	**336**	**4,072,725**	**322**	**3,974,957**	**104**	**1,516,435**

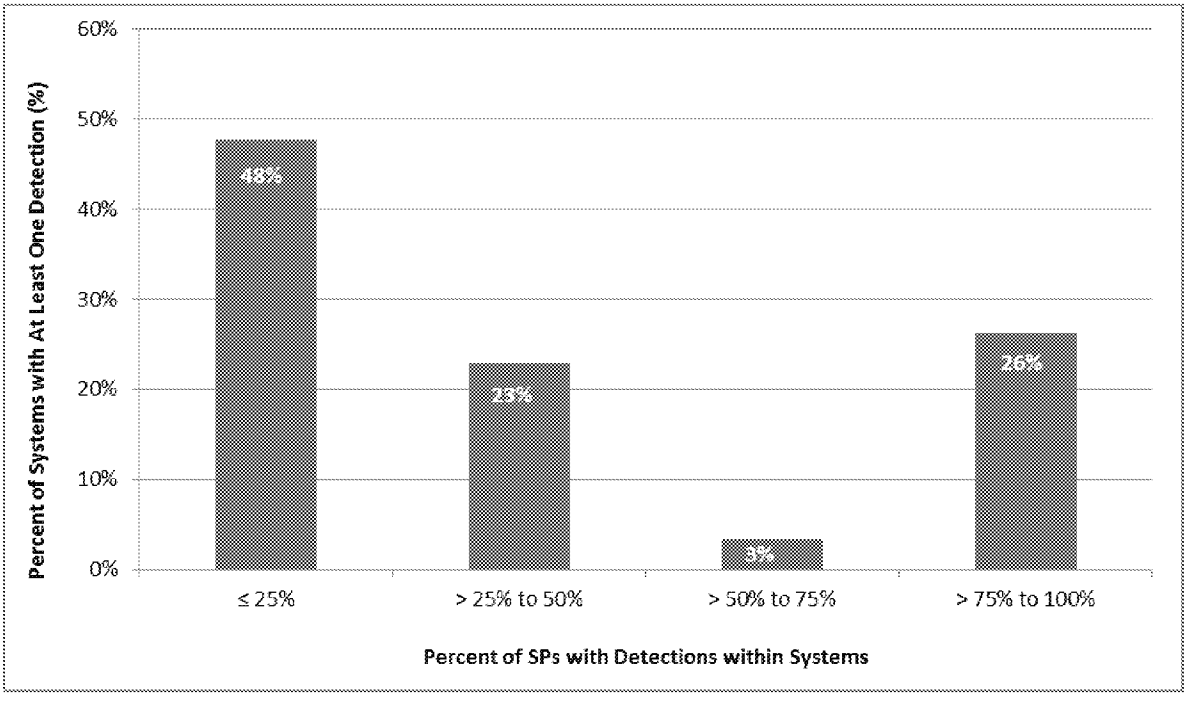
Note: Due to trailing decimal places (not shown in the table) for the population served by ground water and surface water sample points, the counts of total population served may appear to be slightly off.

Exhibit [SEQ Exhibit * ARABIC]: Sample Points With at Least Two Detections and Their Proportional Populations Based on the UCMR 1 Perchlorate Dataset (June 2013 Version)

System Type	Source Water Type	Total UCMR 1 Sample Points	Total UCMR 1 Population	Concentration Thresholds					
				≥ 4 µg/L		> 18 µg/L		> 56 µg/L	
				Number of Sample Points	Proportional Population	Number of Sample Points	Proportional Population	Number of Sample Points	Proportional Population
Small Systems (serving ≤10,000)	Ground Water	1,211	1,939,815	1	56	1	56	0	0
	Surface Water	243	820,755	3	6,123	3	6,123	0	0
	All Systems	**1,454**	**2,760,570**	**4**	**6,179**	**4**	**6,179**	**0**	**0**
Large Systems (serving >10,000)	Ground Water	8,212	53,765,152	31	114,287	31	114,287	4	10,998
	Surface Water	5,270	169,087,949	91	1,123,105	84	1,075,939	25	468,004
	All Systems	**13,482**	**222,853,101**	**122**	**1,237,392**	**115**	**1,190,226**	**29**	**479,002**
All Systems	Ground Water	9,423	55,704,967	32	114,343	32	114,343	4	10,998
	Surface Water	5,513	169,908,704	94	1,129,228	87	1,082,062	25	468,004
	All Systems	**14,936**	**225,613,671**	**126**	**1,243,571**	**119**	**1,196,405**	**29**	**479,002**

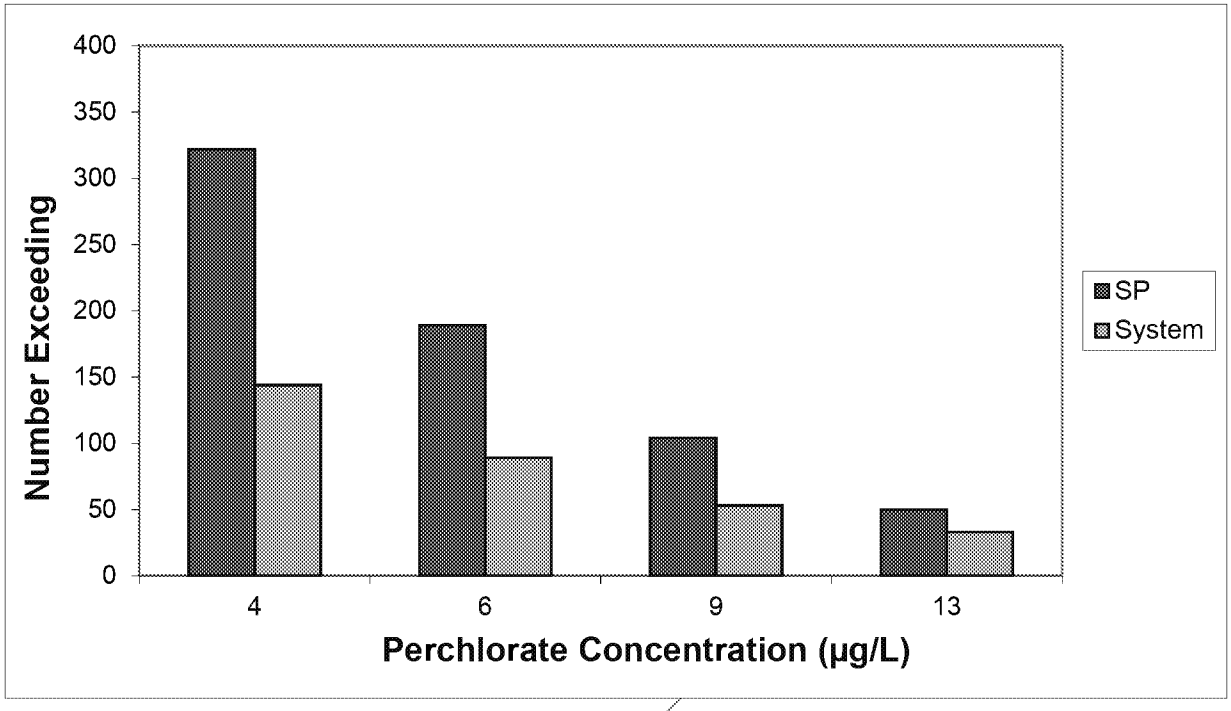
[REF _Ref353883366] shows the proportion of systems detecting perchlorate in various percentages of their sample points. Of the 149 PWSs with at least one detection of perchlorate, nearly half (48%) of the systems had detections in 25% or fewer of their sample points. A little more than half of the systems (52%) had detections in more than one-quarter of their sample points and 29% had detections in more than half of their sample points. (About 20% of all UCMR 1 systems with detections of perchlorate had only 1 sample point.)

Exhibit [SEQ Exhibit * ARABIC]: Portion of Systems with Perchlorate Detections in Various Percentages of System Sampling Points (Among Systems with at Least One Detection) Based on the UCMR 1 Perchlorate Dataset (June 2013 Version)



[REF _Ref316583205] displays the number of PWSs and sample points with at least one detection that exceeded the perchlorate concentration thresholds of 4, 18, and 56 µg/L. A total of 322 sample points at 144 systems had at least one detection greater than 4 µg/L. Fifty sample points at 33 systems had at least one detection greater than 18 µg/L. Note that systems and sample points with exceedances of the higher thresholds are counted multiple times in [REF _Ref316583205] (i.e., systems counted as exceeding 56 µg/L are also counted as exceeding 4, and 18 µg/L).

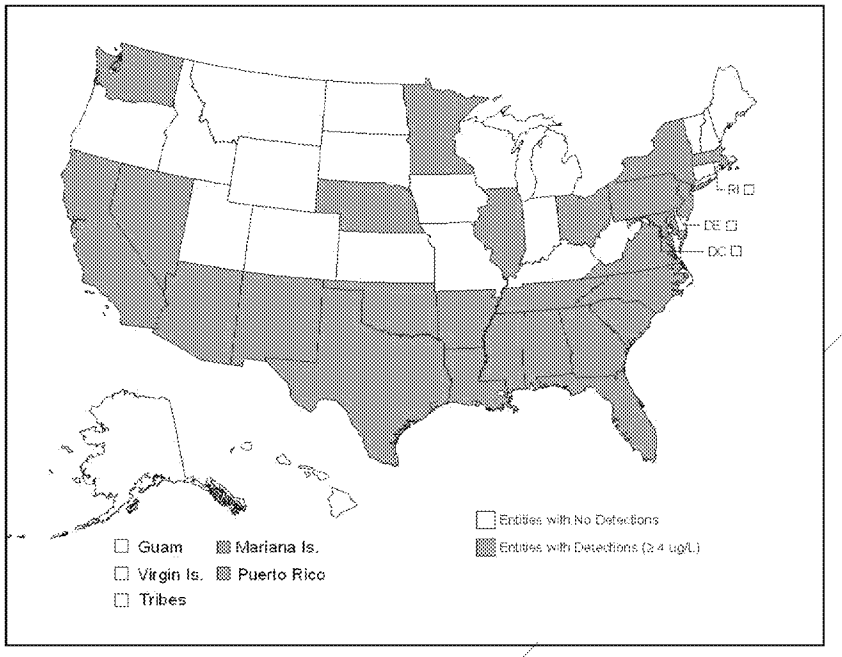
Exhibit [SEQ Exhibit * ARABIC]: Number of UCMR 1 Systems and Sample Points Exceeding Various Concentration Thresholds Based on the UCMR 1 Perchlorate Dataset (June 2013 Version)



4.4 Spatial and Graphical Assessments

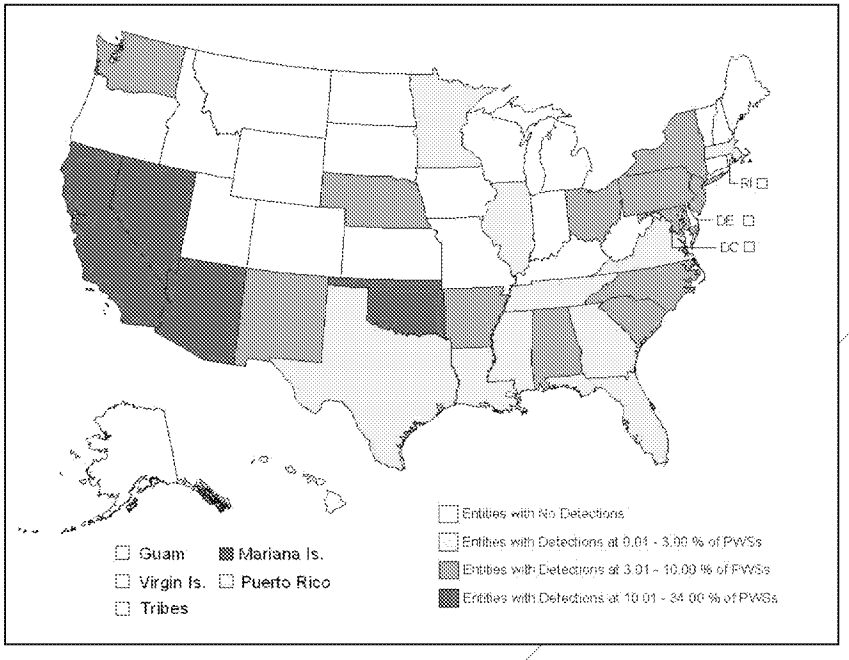
Spatial and graphical assessments of UCMR 1 perchlorate monitoring data are provided in this section. Perchlorate was detected at PWSs in 26 states, Puerto Rico, and the Commonwealth of the Northern Mariana Islands (see [REF _Ref316583235]). EPA identified perchlorate analytical detections in PWSs across states in the southern portion of the country, several states in the Northeast, Washington, Nebraska, Minnesota, Illinois, and Ohio. States with the highest percentage of systems with perchlorate analytical detections were California, Arizona, Nevada, and Oklahoma. The Northern Mariana Islands also had a high proportion of systems with analytical detections (33%), but since only three systems were sampled, this distinction is based on a relatively small sample size. Breakdowns of sampling efforts by state can be found in Appendix E, including state-level (non-parametric) counts of systems and population served by systems; systems (and population served by systems) with detections; and summaries of detected concentrations.

Exhibit [SEQ Exhibit * ARABIC]: Geographic Distribution of Perchlorate – States with At Least One Detection Equal to or Above the MRL (≥ 4 µg/L) Based on the UCMR 1 Perchlorate Dataset (June 2013 Version)



This map depicts UCMR 1 results from both small systems and large systems. (Note: Small and large system data were collected in all states.) As discussed in this report, the statistical selection of UCMR 1 small systems was designed to be representative at the national-level, but not at the state level. Therefore, this map should only be considered an approximation of state-level patterns of contaminant occurrence.

Exhibit [SEQ Exhibit * ARABIC]: Geographic Distribution of Perchlorate – State Percentage of PWSs with At Least One Detection Equal to or Above the MRL (≥ 4 µg/L) Based on the UCMR 1 Perchlorate Dataset (June 2013 Version)



This map depicts UCMR 1 results from both small systems and large systems. (Note: Small and large system data were collected in all states.) As discussed in this report, the statistical selection of UCMR 1 small systems was designed to be representative at the national-level, but not at the state level. Therefore, this map should only be considered an approximation of state-level patterns of contaminant occurrence.

[REF _Ref316583297] provides a map of the locations and concentrations of perchlorate detections in PWSs across the US. The map shows widespread detections of perchlorate across large portions of the United States and also indicates several specific areas of higher numbers, or clusters, of PWSs with detections. Southern California has many PWSs with detections as well as some PWSs with higher concentrations of perchlorate. The San Francisco Bay area in California and the mid-Atlantic region from the Washington, D.C. area to the greater metropolitan New York City area also had many systems with detections. Other areas with somewhat higher numbers of PWSs and/or higher concentrations are in Florida, Oklahoma, and Puerto Rico.

Exhibit [SEQ Exhibit * ARABIC]: System-level Geographic Distribution of Perchlorate – Maximum Concentration of Detections per System Based on the UCMR 1 Perchlorate Dataset (June 2013 Version)

This map depicts UCMR 1 results from both small systems and large systems. The statistical selection of UCMR 1 small systems was designed to be representative at the national level, but not at the state level. Therefore, this map should only be considered an approximation of state-level patterns of contaminant occurrence.

5 Laboratory Analytical Methods

5.1 EPA Methods

EPA has developed five analytical methods for the identification and quantification of perchlorate in drinking water. These methods - 314.0, 314.1, 314.2, 331.0, and 332.0 - have different characteristics, performance, and costs. A description of these methods is presented below.

EPA Method 314.0, "Determination of Perchlorate in Drinking Water Using Ion Chromatography" (Revision 1.0, USEPA, 1999a) reports a method detection limit (MDL) of 0.53 µg/L. Single-laboratory mean percent recoveries in various aqueous matrices range from 86% to 113% with relative standard deviations (RSDs) of 1.0% to 12.8%. A minimum reporting level (MRL) is not specified in the method; however, a range of 3.0 to 5.0 µg/L is cited as a benchmark range for quality assurance/quality control (QA/QC) procedures. The MRL is typically established as either a concentration that is greater than three times the laboratory MDL or at a concentration that yields a response greater than a signal to noise ratio of five. In either case, the MRL must not be below the lowest instrument calibration standard (USEPA, 1999a). Method 314.0 was widely adopted as the standard perchlorate method.

Method 314.0 has the potential for interferences in the determination of perchlorate. EPA developed options for minimizing interferences to mitigate the potential perchlorate misidentification. EPA has identified three types of potential interferences:

- direct chromatographic coelution – an analyte response is observed at very nearly the same retention time (i.e., the "time window" when an analyte emerges from the ion chromatography (IC) column and is "seen" by the detector) as perchlorate;
- concentration dependent coelution – observed when the response of higher than typical concentrations of a neighboring peak (i.e., another compound in the sample) overlap into the retention time window of perchlorate; and
- ionic character displacement – retention times may significantly shift due to the influence of high ionic strength matrices (high mineral content or hardness) overloading the exchange sites in the ion chromatography column and significantly shortening the retention time of perchlorate.

The possibility of interferences and perchlorate misidentification may become greater if reporting levels (RLs) are reduced from EPA's original MRL of 4 µg/L associated with the use of EPA Method 314.0 for perchlorate monitoring under UCMR 1, to 1 µg/L. Sensitivity can be improved by either increasing the sample injection volume or incorporating a smaller diameter analytical column. In both cases, however, column capacity will limit the volume of sample that can be injected on-column without degradation of chromatographic resolution. EPA understood the potential for reduced resolution when setting the UCMR 1 perchlorate MRL at 4 µg/L rather than at a lower concentration.

Massachusetts Department of Environmental Protection reduced the reporting level to 1 µg/L by using lower concentration spiking solutions and standards for laboratory QC (MassDEP, 2004a) along with a series of initial and ongoing quality control requirements and limits (MassDEP, 2006a). The physical modifications made by MassDEP constitute such a significant modification that the modified method can no longer be considered EPA Method 314.0. An increase in sample injection volume and a smaller-bore chromatographic column would reduce the chromatographic resolution of EPA Method 314.0. As a result, the interferences that are identified in EPA Method 314.0 can be exacerbated for higher ionic strength samples with elevated total dissolved solids (TDS) and are more likely to have retention times that can result in falsely assigning these interferences as detections of perchlorate.

EPA believes that the injection and chromatographic conditions specified in EPA's original publication of EPA Method 314.0, along with mitigative steps that are included to reduce interferences, are critical to proper resolution and identification of perchlorate. Therefore, EPA has confidence in the analytical results and the detections found in UCMR 1 monitoring that resulted from the use of EPA Method 314.0 as originally published.

After EPA published Method 314.0, the agency adopted additional method development goals for the analysis of perchlorate in drinking water including: 1) reducing MRL to less than 1 µg/L through the application of sample concentration techniques, microbore analytical columns, and advanced detection systems (i.e., mass spectrometry), 2) further increasing the tolerance for high ionic strength matrices, and 3) enhancing measurement selectivity.

EPA Method 314.1, "Determination of Perchlorate in Drinking Water Using Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection" (Revision 1.0, USEPA, 2005b) documents EPA single-laboratory lowest concentration minimum reporting levels (LCMRLs) of less than 0.2 µg/L (detection limit [DL] = 0.03 µg/L) using online sample pre-concentration. The method uses matrix diversion to handle high ionic strength matrices (up to 1,000 mg/L total dissolved solids [TDS]) and added confirmation analysis using a second analytical column (USEPA, 2005b).

EPA Method 314.2, "Determination of Perchlorate in Drinking Water Using Two-Dimensional Ion Chromatography with Suppressed Conductivity Detection" (USEPA, 2008c) documents EPA single-laboratory LCMRLs of less than 0.1 µg/L (DLs < 0.02 µg/L) using large volume injection. The method uses 2-D chromatography to handle high ionic strength matrices (up to 1,000 mg/L TDS) by isolating perchlorate in the first dimension and measuring it in the second dimension (USEPA, 2008c).

EPA Method 331.0, "Determination of Perchlorate in Drinking Water by Liquid Chromatography Electrospray Ionization Mass Spectrometry" (Revision 1.0, USEPA, 2005c) documents EPA single-laboratory LCMRLs of less than 0.1 µg/L (DLs < 0.01 µg/L), applied multiple analytical advancements to a liquid chromatography (LC) analysis including a perchlorate selective LC column (IonPak AS-21), mass spectrometry (MS) or tandem mass spectrometry (MS/MS) detection for selectivity and sensitivity, and a custom O-18 isotopically labeled internal standard ($Cl^{18}O_4^-$) (USEPA, 2005c).

EPA Method 332.0, "Determination of Perchlorate in Drinking Water by Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry" (USEPA, Revision 1.0, 2005d) documents an EPA single-laboratory LCMRL of 0.1 µg/L (DL = 0.02 µg/L), applied multiple analytical advancements in an IC analysis including suppressed conductivity IC, MS or MS/MS detection for selectivity and sensitivity, and a custom O-18 isotopically labeled internal standard ($Cl^{18}O_4^-$) (USEPA, 2005d).

In May 2012, the California Department of Public Health's Drinking Water and Radiation Laboratory published recommendations regarding the potential for perchlorate degradation in water samples. According to the guidance/recommendation, EPA Methods 314.1, 314.2, 331.0 and 332.0 require that water samples be filtered in the field and kept cold during shipment to the laboratory. EPA Method 314.0 does not include this sample preservation requirement. Since microbial degradation of perchlorate requires anaerobic conditions, field filtration is not necessary when using EPA Method 314.0 provided aerobic conditions are maintained for the samples until analysis. Aerobic conditions can be effected by half-filling sample bottles in the field, agitating them to dissolve air in the samples and then chilling them on ice for delivery to the laboratory (CA EPA, 2016).

It is anticipated that most drinking water samples will be aerobic in nature and will not become anaerobic prior to analysis within the 28-day holding time specified in EPA Method 314.0. Any air in the headspace of a sample to be analyzed by EPA Method 314.0 will support aeration of the sample due to agitation during shipping. EPA Method 314.0 indicates that perchlorate has been shown to be stable for at least 28 days.

[REF _Ref366605474] compares the five EPA analytical methods for the analysis of perchlorate in drinking water.

Exhibit [SEQ Exhibit * ARABIC]: Comparison of EPA Analytical Methods for the Analysis of Perchlorate in Drinking Water

Method	LCMRL or MRL[1] (µg/L)	MDL/DL (µg/L)	Perchlorate Retention Time (minutes)	Demonstrates Acceptable Performance in 1,000 mg/L TDS	Confirmation	Complexity
314.0	4.0 (MRL)	0.53	11	No[10]	Matrix Spike Assessment	Moderate
314.1	0.13 - 0.14	0.03	30-35	Yes	Second Column Analysis	Moderate
314.2	0.038 - 0.06	0.012- 0.018	37	Yes	2-D	High
331.0	0.022 (MS/MS) 0.056 (Selected Ion Monitoring [SIM])	0.005 (MS/MS) 0.008 (SIM)	9	Yes	MS/MS or MS	Moderate

[10] EPA Method 314.0 was demonstrated to provide acceptable performance for samples up to 600 – 700 TDS using the AG16/AS16 analytical column

Method	LCMRL or MRL[1] (µg/L)	MDL/DL (µg/L)	Perchlorate Retention Time (minutes)	Demonstrates Acceptable Performance in 1,000 mg/L TDS	Confirmation	Complexity
332.0	0.10 (SIM)	0.02	8	Yes	MS	Moderate

[1] Value for EPA Method 314.0 is a "national" MRL for perchlorate monitoring conducted under UCMR 1. Remaining values are for EPA's single-laboratory LCMRLs generated during method development. MRLs have not been established for EPA Methods 314.1, 314.2, 331.0, and 332.0.

5.2 Methods Used by States

EPA Methods 314.0, 314.1, 314.2, 331.0, and 332.0 underwent EPA's analytical method development and validation processes. The validation process includes a protocol for modifications to any existing EPA-approved analytical methods and a protocol for new determinative techniques. Both validation protocols are rigorous and consider many technical aspects of analytical method performance, (USEPA, 1999b; USEPA, 1999c) including:

- Detection limits;
- Instrument calibration;
- Precision and analyte recovery;
- Analyte retention times;
- Contamination in blanks;
- Development of Quality Control Acceptance Criteria;
- Analysis of field samples; and
- Other technical aspects of sample analysis and data reporting.

UCMR 1 required PWSs to conduct assessment monitoring for perchlorate using method 314.0. In 2004, MassDEP began to evaluate laboratory performance for the analysis of perchlorate in drinking water (MassDEP, 2004a; 2004b). MassDEP indicated use of a modified EPA Method 314.0 to achieve a reporting level of 1.0 µg/L (MassDEP wanted reliable laboratory performance to extend below what was to become their drinking water standard of 2.0 µg/L in 2006). The modifications include the use of lower spiking, lower concentration standard solutions, and an initial and on-going quality control protocol (MassDEP, 2004a; 2006a). In 2006, MassDEP published a data set of confirmed perchlorate detections above 1.0 µg/L (MassDEP, 2006b). These data were generated in 2004, 2005 and early 2006. Although the analytical method is not specified in MassDEP (2006b), presumably a modified version of EPA Method 314.0 was used.

By 2007, MassDEP had included EPA Methods 314.1, 331.0 and 332.0 as acceptable methods for the analysis of perchlorate in DW (MassDEP, 2007), indicating that these methods could achieve reliable quantitation at or below 1.0 µg/L. The single-laboratory LCMRLs for these three methods are listed in [REF _Ref366605474].

Note that EPA Method 314.2 was not published until 2008. The single-laboratory LCMRLs for EPA Method 314.2 are 0.038-0.060 µg/L. These LCMRLs are specific to EPA's method development laboratory. In consideration of natural variability in laboratory performance

nationwide, MRLs for EPA Methods 314.1, 314.2, 331.0 and 332.0 would possibly be less than 1.0 µg/L. MRLs have not been determined for these methods because these methods have not been selected for use in a national regulatory program. Thus, reliable quantitation in the sub-µg/L range should be attainable using EPA Methods 314.1, 314.2, 331.0, and/or 332.0 while reliable quantitation using EPA Method 314.0 is possible only at or above approximately 4 µg/L to minimize the potential for false positives.

A review of available state data for perchlorate (i.e., California, Illinois, Massachusetts and Ohio) indicates the predominant use of EPA Method 314.0, although limited use of 314.1 and 331.0 is indicated by the State of Massachusetts. California perchlorate monitoring data indicates the use of methods "314" and "331."

5.3 Laboratory Analysis Cost Estimates

EPA compiled cost estimates for perchlorate analytical methods by asking laboratories to provide a low-to-high price range that they might charge for running perchlorate methods. In April of 2018, three laboratories were contacted. The estimates, summarized in [REF _Ref526572158 \h], vary depending on the quantity of samples submitted for analysis, target reporting levels and other analytical complexities or contractual factors.

Exhibit [SEQ Exhibit * ARABIC]: Cost Estimates of Laboratory Analytical Methods for Perchlorate

EPA Perchlorate Method	Low Estimate Per Analysis	High Estimate Per Analysis	Notes *
EPA METHOD 314.0	$55	$65	Range is based on information from two of the three laboratories contacted.
EPA METHOD 314.1	--	--	None of the labs contacted run this method.
EPA METHOD 314.2	--	--	None of the labs contacted run this method.
EPA METHOD 331.0	$90	$175	Range is based on information from two of the three laboratories contacted.
EPA METHOD 332.0	$175	$175	Estimate is based on information from one of the three laboratories contacted.

* Sample analysis cost may depend on the number of samples submitted and the turnaround time requested.

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United States
Environmental Protection
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Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water

Volume I

November 2018

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Abbreviations and Acronyms

ADHD	Attention deficit/hyperactivity disorder
ANOVA	Analysis of variance
ANT	Amsterdam Neuropsychological Test
ASD	Autism spectrum disorder
ATA	American Thyroid Association
ATSDR	Agency for Toxic Substances and Disease Registry
BBDR	Biologically based dose-response
BMI	Body mass index
BSID	Bayley Scales of Infant Development
bw	Body weight
CBCL	Child Behavior Checklist
CCL	Contaminant Candidate List
CI	Confidence interval
CMD	Coefficient of mental development
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
FiPS-S	Finnish Prenatal Study of Schizophrenia
FMC	Finnish Maternity Cohort
FSIQ	Full-scale IQ
fT3	Free triiodothyronine
fT4	Free thyroxine
GW	Gestational week(s)
hCG	Human chorionic gonadotropin
HPT	Hypothalamic-pituitary-thyroid
HRL	Health reference level
IQ	Intelligence quotient
IQR	Interquartile range
LDL	Low-density lipoprotein
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MDI	Mental Development Index (of the BSID)
MRI	Magnetic resonance imaging
MRL	Method reporting limit
MS	Mass spectrometry
NEPSY	Developmental Neuropsychological Assessment
NHANES	National Health and Nutrition Examination Survey
NIS	Sodium-iodide symporter
NOAEL	No observed adverse effects level
NRC	National Research Council
NSAID	Non-steroidal anti-inflammatory drug
OHAT	Office of Health Assessment and Translation
OR	Odds ratio
PBDE	Polybrominated diphenyl ether
PBPK/PD	Physiologically based pharmacokinetic/pharmacodynamic
PC	Partition coefficient
PCB	Polychlorinated biphenyl
PDI	Psychomotor Development Index (of the BSID)
PDP	Pervasive Developmental Problems Scale
PFA	Perfluorinated acid

PIQ	Performance IQ
PPVT	Peabody Picture and Vocabulary Test
RBC	Red blood cell
RfD	Reference dose
ROB	Rest-of-body or risk-of-bias
RR	Relative risk
RSC	Relative source contribution
SAB	Science Advisory Board
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SDWA	Safe Drinking Water Act
SE	Standard error
SRS	Social Responsiveness Scale
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine-binding globulin
Tg	Thyroglobulin
TgAb	Thyroglobulin antibody
THoP	Transient hypothyroxinemia of prematurity
TPO Ab	Thyroid peroxidase antibody
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone (or thyrotropin)
tT3	Total triiodothyronine
tT4	Total thyroxine
TTR	Transthyretin
VIQ	Verbal IQ
VRM	Visual Recognition Memory
WISC	Wechsler Intelligence Scale for Children
WRAVMA	Wide Range Assessment of Visual Motor Ability

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Executive Summary

The EPA is developing approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate in accordance with recommendations made by the Agency's Science Advisory Board (SAB). The EPA has developed and peer reviewed both a biologically based dose-response (BBDR; also known as a physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD)) model that predicts the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages and the approach to connect the output of the BBDR model to neurodevelopmental outcomes using the epidemiological literature.

The purpose of this document is to present the revisions to the BBDR model and alternative approaches that link the revised perchlorate BBDR model predictions to neurodevelopmental effects in response to the prior peer reviews. The document does not derive an MCLG; rather, it presents alternative approaches that might be used to inform future decisions including the derivation of an MCLG in accordance with the Safe Drinking Water Act (SDWA).

MCLGs are non-enforceable, health-based goals that the EPA sets for each regulated drinking water contaminant. In accordance with SDWA, they are set at a level at which no known or anticipated adverse human health effect would occur and to allow for an adequate margin of safety. MCLGs consider only public health, and not limits of analytical measurement and treatment technology effectiveness. SDWA requires that the EPA establish the enforceable Maximum Contaminant Level (MCL) as close as feasible to the MCLG taking costs and benefits into consideration.

In 2012, as a part of the National Primary Drinking Water Regulation development process for perchlorate and in accordance with the requirements of SDWA, the EPA sought recommendations from the SAB on approaches to inform the derivation of a perchlorate MCLG.

In 2013, the SAB recommended the following:

- Derive a perchlorate MCLG that addresses sensitive life stages through PBPK/PD modeling;
- "Expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- Utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition to thyroid hormone changes and finally neurodevelopmental impacts; [and]
- Extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB, 2013, p. 19).

The SAB stated that this data-driven approach represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages than is possible with the default approach for deriving an MCLG, and that the EPA should also consider available data on potential adverse health effects (neurodevelopmental outcomes) due to perturbations in thyroid hormone levels regardless of the cause of those perturbations (SAB, 2013).

Based on the SAB's recommendations, the EPA, with contributions from the Food and Drug Administration, developed a BBDR model to predict the effect of perchlorate on the thyroid gland in formula-fed and breastfed infants, and in lactating women. This draft model was integrated with a previously published model that similarly predicted the effects of perchlorate on serum thyroid hormone concentrations in the third-trimester pregnant woman and her fetus. The model was subjected to external peer review in January 2017. The final peer review report titled *External Peer Review for EPA's Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water* is available through the docket at [HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0439-0006"].

The EPA considered all of the peer reviewers' recommendations from the January 2017 peer review and focused on those that were anticipated to be most important for increasing the scientific rigor of the model and modeling results. These revisions are summarized in Section [REF _Ref482972651 \r \h] of this report; additional detail is available in Appendix A. Model revisions focused on the following key recommendations:

- Extending the model to early pregnancy;
- Incorporating biological feedback control of hormone production via thyroid-stimulating hormone or thyrotropin (TSH) signaling, such that the model can describe lower levels of iodide nutrition;
- Calibrating the model and evaluating its behavior for upper and lower percentiles of the population, as well as the population median; and
- Conducting an uncertainty analysis for key parameters.

The EPA has developed a two-stage approach linking the revised BBDR model results ("stage 1") with quantitative information on neurodevelopmental outcomes from epidemiological studies ("stage 2"). EPA has also developed an alternative population-based approach that uses the revised BBDR model to evaluate a shift in the population of pregnant women who could be hypothyroxinemic.[1]

The first stage of the two-stage approach is the development of the revised BBDR model that describes thyroidal hormone production in women of childbearing age with low/adequate iodine intake and predicts the relationship between perchlorate exposure and changes in thyroid hormone levels in early pregnancy. The available data for the second stage of the analysis comes from epidemiological studies that evaluated maternal thyroid hormone levels in early pregnancy and neurodevelopmental outcomes (these are not studies evaluating perchlorate exposure). The EPA presents and characterizes all of these studies in Section [REF _Ref488740188 \r \h] of this report.

Using the output from the revised BBDR model and the quantitative relationships between thyroid hormone levels and neurodevelopmental effects from the published epidemiological studies, the EPA characterized the relationship between perchlorate exposure on free T4 (fT4) levels in pregnant

[1] Serum free thyroxine (fT4) value at the lower end of the normal range with normal levels of serum TSH, as opposed to hypothyroidism, which consists of low levels of serum fT4 levels and high levels of serum TSH. For the purposes of this report, fT4 and TSH values will be assumed to be measured via the serum unless otherwise stated.

mothers during early gestation and the potential for changes in neurodevelopmental outcomes in their offspring.

The EPA's alternative population-based approach estimates the shift in the population of hypothyroxinemic, pregnant women that would result from perchlorate exposure. The EPA used the BBDR model predictions to estimate the proportion of hypothyroxinemic pregnant mothers in the population, assuming a distribution of fT4 levels with a consistent iodine intake.

These approaches were peer reviewed in January 2018. Based on recommendations from the peer review panel, the following updates to the first draft of this report have been made:

- Reevaluated the derivation of the distribution of fT4 values output by the BBDR model.
- Updated the literature search to include studies between the last literature review and the peer review.
- Reevaluated the exclusion of identified literature from dose-response analysis for the relationship between fT4 and neurodevelopment.
- Evaluated the quality of studies with information on the dose-response relationship between thyroid hormones and neurodevelopment.
- Reanalyzed the dose-response information relating maternal thyroid hormone levels to IQ from the data provided by Dr. Korevaar.

The updates were made to increase the rigor of the approaches presented. The overall impression from the peer review was supportive of the methods presented in the first draft of this document as evidenced by the following quote:

"The panel commends EPA for the substantial amount of work done in creating the new modeling and preparing the report under review. It was highly responsive to the review comments from a year ago. Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer review report], the current models are fit-for-purpose to determine an MCLG" [ADDIN EN.CITE <EndNote><Cite><Author>External Peer Reviewers for U.S. EPA</Author><Year>2018</Year><RecNum>1974</RecNum><Pages>2</Pages><DisplayText>(EPA, 2018, p. 2)</DisplayText><record><rec-number>1974</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1521552479">1974</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>External Peer Reviewers for U.S. EPA</author></authors><secondary-authors><author>Versar Inc. for U.S. EPA</author></secondary-authors></contributors><titles><title>External peer review for U.S. EPA's proposed approaches to inform the derivation of a maximum contaminant level goal for perchlorate in drinking water</title></titles><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>]

1. Introduction

The EPA is developing approaches to inform the derivation of a Maximum Contaminant Level Goal (MCLG) for perchlorate. The EPA has developed and peer reviewed a biologically based dose-response (BBDR; also known as a PBPK/PD) model that predicts the relationship between perchlorate exposure and thyroid hormone levels in sensitive life stages. This document presents revisions made to the BBDR model and approaches that link the revised perchlorate BBDR model predictions to neurodevelopmental effects in response to the prior peer reviews.

1.1 Background on Perchlorate

Perchlorate has both natural and manmade sources. It is formed naturally via atmospheric processes and can be found within mineral deposits in certain geographical areas, particularly those with arid environments [ADDIN EN.CITE <EndNote><Cite><Author>Trumpolt</Author><Year>2005</Year><RecNum>114</RecNum><DisplayText>(Trumpolt et al., 2005)</DisplayText><record><rec-number>114</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465913666">114</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Trumpolt, Clayton W</author><author>Crain, Michael</author><author>Cullison, Geoffrey D</author><author>Flanagan, Susan JP</author><author>Siegel, Lenny</author><author>Lathrop, Stephen</author></authors></contributors><titles><title>Perchlorate: sources, uses, and occurrences in the environment</title><secondary-title>Remediation: The Journal of Environmental Cleanup Costs, Technologies, & Techniques</secondary-title></titles><periodical><full-title>Remediation: The Journal of Environmental Cleanup Costs, Technologies, & Techniques</full-title></periodical><pages>65-89</pages><volume>16</volume><number>1</number><dates><year>2005</year></dates><urls></urls></record></Cite></EndNote>]. In the past, nitrate fertilizers from Chilean deposits that contained perchlorate were widely used in the United States, which resulted in perchlorate contamination of soil and plants (Agency for Toxic Substances and Disease Registry (ATSDR), 2008). An additional source of perchlorate currently in the environment is from the production and usage of rocket fuel, by both the defense and aerospace industries (National Research Council, 2005). Perchlorate is also generated during the manufacture and use of pyrotechnic devices such as fireworks [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>]. It is difficult to determine the annual production of perchlorate in these industries, as perchlorate is not included on the EPA's Toxics Release Inventory list of chemicals that must be reported. In 1994, annual production of perchlorate was estimated to be approximately 22 million pounds [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><Dis

playText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>].

1.1.1 Chemical Identity of Perchlorate

Perchlorate is a negatively charged ion that is composed of one chlorine atom and four oxygen atoms and is released to the environment in the form of a salt (a type of ionic compound) [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>]. The most common perchlorate salt produced in the United States is ammonium perchlorate, with magnesium, potassium, sodium, and lithium perchlorate also generated in substantial amounts [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>]. Perchlorate is highly stable and mobile in the aqueous environment, since the perchlorate salts are very soluble in water and do not adsorb to soil or sediment [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>]. Because of their

low vapor pressure, perchlorate salts do not volatilize into the air from water [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>].

1.1.2 Overview of Human Exposure and Health Effects

Humans are primarily exposed to perchlorate from ingestion of contaminated food and drinking water supplies [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>]. The EPA's analysis of nationally representative data from the first Unregulated Contaminant Monitoring Rule found that 4.1% of 3,865 public water systems tested for perchlorate had concentrations above the method reporting limit (MRL) of 4 µg/L. [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2008</Year><RecNum>121</RecNum><DisplayText>(U.S. EPA, 2008)</DisplayText><record><rec-number>121</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465916938">121</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Interim drinking water health advisory for perchlorate</title></titles><dates><year>2008</year></dates><pub-location>Washington, D.C.</pub-location><isbn>EPA 822-R-08-025</isbn><urls><related-urls><url><style face="underline" font="default" size="100%">https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1004X7Q.TXT</style></url></related-urls></urls></record></Cite></EndNote>]. The average concentration of perchlorate in samples above the MRL was 9.85 µg/L, with a maximum concentration of 420 µg/L [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2008</Year><RecNum>121</RecNum><DisplayText>(U.S. EPA, 2008)</DisplayText><record><rec-number>121</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465916938">121</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Interim drinking water health advisory for

perchlorate</title></titles><dates><year>2008</year></dates><pub-location>Washington, D.C.</pub-location><isbn>EPA 822-R-08-025</isbn><urls><related-urls><url><style face="underline" font="default" size="100%">https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1004X7Q.TXT</style></url></related-urls></urls></record></Cite></EndNote>]. In an analysis of foods from the U.S. Food and Drug Administration's (FDA's) Total Diet Study, approximately three-quarters of the foods tested had at least one sample with detectable levels of perchlorate [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Dietary sources with detectable levels of perchlorate include, but are not limited to, cow's milk, breast milk, and lettuce [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Ingestion exposures are of concern because perchlorate is easily and almost completely absorbed from the gastrointestinal tract [ADDIN EN.CITE <EndNote><Cite><Author>Srinivasan</Author><Year>2009</Year><RecNum>118</RecNum><DisplayText>(Srinivasan & Viraraghavan, 2009)</DisplayText><record><rec-number>118</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465916062">118</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Srinivasan, Asha</author><author>Viraraghavan, Thiruvenkatachari</author></authors></contributors><titles><title>Perchlorate: Health effects and technologies for its removal from water resources</title><secondary-title>International Journal of Environmental Research and Public Health</secondary-title></titles><periodical><full-title>International journal of environmental research and public health</full-title></periodical><pages>1418-1442</pages><volume>6</volume><number>4</number><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. In a 2004-2005 perchlorate dietary exposure study, FDA estimated the average dietary perchlorate exposure for all persons aged 2 and above at 0.053 µg/kg bw/day [ADDIN EN.CITE <EndNote><Cite><Author>FDA</Author><Year>2015</Year><RecNum>1916</RecNum><DisplayText>(Food and Drug Administration (FDA), 2015)</DisplayText><record><rec-number>1916</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519436">1916</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>Food and Drug Administration (FDA),</author></authors></contributors><titles><title>Preliminary estimation of perchlorate dietary exposure based on FDA 2004/2005 exploratory data</title></titles><dates><year>2015</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">https://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077653.htm</style></url></related-urls></urls></record></Cite></EndNote>]. In 2016, FDA estimated that average perchlorate dietary intake for the total U.S. population had increased from its previous assessment and ranged between 0.13 and 0.15 µg/kg bw/day, with estimated average intakes ranging between 0.09 and 0.48 µg/kg bw/day based on age [ADDIN EN.CITE <EndNote><Cite><Author>Abt</Author><Year>2016</Year><RecNum>1917</RecNum><DisplayText>(Abt, Spungen, Pouillot, Gamalo-Siebers, & Wirtz, 2016)</DisplayText><record><rec-number>1917</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519671">1917</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Abt, E.</author><author>Spungen, J.</author><author>Pouillot, R.</author><author>Gamalo-Siebers, M.</author><author>Wirtz, M.</author></authors></contributors><titles><title>Update on dietary

intake of perchlorate and iodine from U.S. Food and Drug Administration's Total Diet Study: 2008–2012</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. Inhalation and dermal exposures to perchlorate in the general population are considered to be negligible due to perchlorate's low potential for volatilization and for absorption from the skin [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>]. However, occupational exposures to perchlorate via inhalation of perchlorate dust or deposition into the mouth may occur [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>].

Blount et al. (2006) measured perchlorate in urine samples collected from a sample of U.S. residents as part of the 2001-2002 National Health and Nutrition Examination Survey (NHANES). Blount et al. (2006) detected perchlorate at concentrations greater than 0.05 µg/L in all urine samples tested, with a median concentration of 3.6 µg/L (95th percentile at 14 µg/L). Women of reproductive age (15-44 years) had a median urinary perchlorate concentration of 2.9 µg/L (95th percentile at 13 µg/L). The demographic with the highest concentration of urinary perchlorate was children (6-11 years), who had a median urinary perchlorate concentration of 5.2 µg/L. Blount et al. (2006) estimated a total daily perchlorate dose for the NHANES participants aged 20 and older and found a median dose of 0.066 µg/kg/day and estimated a 95th percentile dose of 0.234 µg/kg/day. A study analyzing perchlorate exposure trends using NHANES cohorts from 2005-2014 found that urinary perchlorate concentrations ranged from 2.63 ng/mL to 3.86 ng/mL, with urinary perchlorate decreasing over this time period [ADDIN EN.CITE <EndNote><Cite><Author>Corey</Author><Year>2017</Year><RecNum>1918</RecNum><DisplayText>(Corey, Bell, & Pleus, 2017)</DisplayText><record><rec-number>1918</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503519754">1918</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Corey, L.</author><author>Bell,

G.P.</author><author>Pleus, R.C.</author></authors></contributors><titles><title>Exposure of the U.S. population to nitrate, thiocyanate, perchlorate, and iodine based on NHANES 2005–2014</title><secondary-title>Bulletin of Environmental Contamination and Toxicology</secondary-title></titles><periodical><full-title>Bulletin of Environmental Contamination and Toxicology</full-title></periodical><pages>83-88</pages><volume>99</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>].

The main target organ for perchlorate's toxicity is the thyroid gland [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>]. Specifically, perchlorate competes with iodide[2] for transport through the sodium-iodide symporter (NIS) into the thyroid gland, which is a necessary step in the production of thyroid hormones Triiodothyronine (T3) and Thyroxine (T4) [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>]. Therefore, perchlorate may lead to decreases in levels of these hormones [ADDIN EN.CITE ADDIN EN.CITE.DATA] by decreasing iodide uptake. Thyroid hormones are essential to the growth and development of fetuses, infants, and young children, as well as to metabolism and energy regulation throughout the lifespan [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-

[2] For the purposes of this report, "iodine" will be used to refer to dietary intake before entering the body. Once in the body, "iodide" will be used to refer to the ionic form.

urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>]. Disturbances in thyroid levels can adversely affect systems throughout the body, including the cardiovascular, pulmonary, and reproductive systems [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>]. Due to their critical role in the development and maintenance of body systems, thyroid hormones are well regulated in order to keep levels within a narrow range.

Reductions in thyroid hormone synthesis due to perchlorate exposures are also expected to lead to increases in thyroid-stimulating hormone or thyrotropin (TSH), a biomarker of thyroid hormone insufficiency as a result of diminished negative feedback [ADDIN EN.CITE <EndNote><Cite><Author>Mattie</Author><Year>2006</Year><RecNum>120</RecNum><DisplayText>(Mattie, Strawson, & Zhao, 2006)</DisplayText><record><rec-number>120</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465916467">120</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Mattie, David R</author><author>Strawson, Joan</author><author>Zhao, Jay</author></authors></contributors><titles><title>Perchlorate toxicity and risk assessment.</title><secondary-title>Perchlorate</secondary-title></titles><pages>169-196</pages><dates><year>2006</year></dates><publisher>Springer</publisher><isbn>0387311149</isbn><urls></urls></record></Cite></EndNote>]. Several short-term (2-week exposure duration) studies have reported that exposures to higher doses of perchlorate in the general population were associated with decreases in iodide uptake, but not with changes in levels of thyroid hormones in the blood [ADDIN EN.CITE ADDIN EN.CITE.DATA]. However, it must be noted that, because the adult euthyroid human thyroid contains several months of T4 stored in the colloid, it is not expected that a 2-week study would result in a change in thyroid status (Dunn & Dunn, 2000, and Brabant et al., 1992, both as cited in Greer et al., 2002).

One small (n = 13), longer-term clinical trial with six-months of perchlorate ingestion at rates of 0.5 or 3 mg of perchlorate ingestion per day did not see any changes in thyroid function [ADDIN EN.CITE <EndNote><Cite><Author>Braverman</Author><Year>2006</Year><RecNum>225</RecNum><DisplayText>(L Braverman et al., 2006)</DisplayText><record><rec-number>225</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468246163">225</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Braverman, L</author><author>Pearce, E.N.</author><author>He, X.</author><author>Pino, S.</author><author>Seeley, M.</author><author>Beck, B.</author><author>Magnani, B.</author><author>Bleunt, B.C.</author><author>Firek, A.</author></authors></contributors><titles><title>Effects of six

months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2721-94</pages><volume>91</volume><number>7</number><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>]. However, urinary iodide levels among participants in this study were considerably higher than the national average (mean 257.8 µg/total volume before 0.5 mg dose of perchlorate; mean 311.5 µg/total volume before 3 mg dose of perchlorate), which could be protective. This is consistent with evidence that healthy adults may be protected against the thyroid hormone changes associated with perchlorate exposures given adequate dietary iodine intake [ADDIN EN.CITE <EndNote><Cite><Author>ATSDR</Author><Year>2008</Year><RecNum>115</RecNum><DisplayText>(ATSDR, 2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human Services</publisher><urls></urls></record></Cite></EndNote>].

Somewhat contradictory to these clinical exposure studies are several more recent epidemiological studies that have found associations between low levels of urinary perchlorate and TSH increases and T4 decreases [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Specifically, Blount et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"t37noWxV","properties":{"formattedCitation":"(2006)","plainCitation":"(2006)"},"citationItems":[{"id":2261,"uris":["http://zotero.org/groups/945096/items/UW4TFPNI"],"uri":["http://zotero.org/groups/945096/items/UW4TFPNI"],"itemData":{"id":2261,"type":"article-journal","title":"Urinary Perchlorate and Thyroid Hormone Levels in Adolescent and Adult Men and Women Living in the United States","container-title":"Environmental Health Perspectives","source":"CrossRef","URL":"http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1764147/","DOI":"10.1289/ehp.9466","ISSN":"0091-6765","language":"en","author":[{"family":"Blount","given":"Benjamin C."},{"family":"Pirkle","given":"James L."},{"family":"Osterloh","given":"John D."},{"family":"Valentin-Blasini","given":"Liza"},{"family":"Caldwell","given":"Kathleen L."}],"issued":{"date-parts":[["2006"]]},"accessed":{"date-parts":[["2017",4,12]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] found women with low urinary iodide to be particularly susceptible to altered thyroid hormone levels with perchlorate exposures. Additionally, Steinmaus et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Df2fZpGA","properties":{"formattedCitation":"(2013)","plainCitation":"(2013)"},"citationItems":[{"id":2292,"uris":["http://zotero.org/groups/945096/items/35VPNIKR"],"uri":["http://zotero.org/groups/945096/items/35VPNIKR"],"itemData":{"id":2292,"type":"article-journal","title":"Combined Effects of Perchlorate, Thiocyanate, and Iodine on Thyroid Function in the National Health and Nutrition Examination Survey 2007-8","container-title":"Environmental research","volume":"123","source":"www.ncbi.nlm.nih.gov","abstract":"Perchlorate, thiocyanate, and low iodine intake can all decrease iodide intake into the thyroid gland. This can reduce thyroid

hormone production since iodide is a key component of thyroid hormone. Previous research has suggested that each of these factors ...","URL":"https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857960/","DOI":"10.1016/j.envres.2013.01.005","note":"PMID: 23473920","language":"en","author":[{"family":"Steinmaus","given":"Craig"},{"family":"Miller","given":"Mark D."},{"family":"Cushing","given":"Lara"},{"family":"Blount","given":"Benjamin C."},{"family":"Smith","given":"Allan H."}],"issued":{"date-parts":[["2013",5]]},"accessed":{"date-parts":[["2017",5,5]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] found an inverse relationship between thyroid hormone levels and perchlorate, and determined populations with concomitant exposures to other goitrogens (i.e., smokers) and low urinary iodide had an increased risk of altered thyroid hormone levels with perchlorate exposure. Furthermore, Steinmaus et al. (2016) evaluated a large pregnant population with early pregnancy exposure to perchlorate and found exposure to perchlorate to be associated with decreased fT4 and T4 and increased TSH.

Exposures to perchlorate and resulting changes in thyroid hormone levels may lead to adverse health effects, particularly in sensitive populations such as pregnant women, fetuses, and infants [ADDIN EN.CITE <EndNote><Cite><Author>Taylor</Author><Year>2014</Year><RecNum>119</RecNum><DisplayText>(Taylor et al., 2014)</DisplayText><record><rec-number>119</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465916379">119</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Taylor, P</author><author>Okosieme, Onyebuchi E</author><author>Murphy, Rhian</author><author>Hales, C</author><author>Chiusano, Elisabetta</author><author>Maina, Aldo</author><author>Joomun, Mohamed</author><author>Bestwick, Jonathan P</author><author>Smyth, Peter</author><author>Paradice, Ruth</author></authors></contributors><titles><title>Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring: data from the controlled antenatal thyroid study</title><secondary-title>The Journal of Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>The Journal of Clinical Endocrinology & Metabolism</full-title></periodical><pages>4291-4298</pages><volume>99</volume><number>11</number><dates><year>2014</year></dates><isbn>0021-972X</isbn><urls></urls></record></Cite></EndNote>]. Thyroid hormones are critical to neurodevelopment of the fetus, and requirements for these hormones increase during pregnancy [ADDIN EN.CITE <EndNote><Cite><Author>Leung</Author><Year>2010</Year><RecNum>117</RecNum><DisplayText>(Leung, Pearce, & Braverman, 2010)</DisplayText><record><rec-number>117</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465915921">117</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leung, A. M.</author><author>Pearce, E N</author><author>Braverman, L</author></authors></contributors><titles><title>Perchlorate, iodine and the thyroid</title><secondary-title>Best Practice & Research Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>Best Practice & Research Clinical Endocrinology & Metabolism</full-title></periodical><pages>133-141</pages><volume>24</volume><number>1</number><dates><year>2010</year></dates><isbn>1521-690X</isbn><urls></urls></record></Cite></EndNote>]. Taylor et al. [ADDIN EN.CITE

<EndNote><Cite ExcludeAuth="1"><Author>Taylor</Author><Year>2014</Year><RecNum>119</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>119</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465916379">119</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Taylor, P</author><author>Okosieme, Onyebuchi E</author><author>Murphy, Rhian</author><author>Hales, C</author><author>Chiusano, Elisabetta</author><author>Maina, Aldo</author><author>Joomun, Mohamed</author><author>Bestwick, Jonathan P</author><author>Smyth, Peter</author><author>Paradice, Ruth</author></authors></contributors><titles><title>Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring: data from the controlled antenatal thyroid study</title><secondary-title>The Journal of Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>The Journal of Clinical Endocrinology & Metabolism</full-title></periodical><pages>4291-4298</pages><volume>99</volume><number>11</number><dates><year>2014</year></dates><isbn>0021-972X</isbn><urls></urls></record></Cite></EndNote>] found that mothers in the upper 10th percentile of perchlorate exposure during pregnancy had significantly increased odds of having offspring with intelligence quotient (IQ) scores in the lowest 10% of the population.

In addition, breastfed infants are completely dependent upon breast milk to provide iodine. Perchlorate exposures can lead to decreases in thyroid hormone levels in infants indirectly by decreasing iodine levels in breast milk or directly by decreasing hormone synthesis in infants, thereby leading to deficits in intellectual function [ADDIN EN.CITE <EndNote><Cite><Author>Leung</Author><Year>2010</Year><RecNum>117</RecNum><DisplayText>(Leung et al., 2010)</DisplayText><record><rec-number>117</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465915921">117</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leung, A. M.</author><author>Pearce, E N</author><author>Braverman, L</author></authors></contributors><titles><title>Perchlorate, iodine and the thyroid</title><secondary-title>Best Practice & Research Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>Best Practice & Research Clinical Endocrinology & Metabolism</full-title></periodical><pages>133-141</pages><volume>24</volume><number>1</number><dates><year>2010</year></dates><isbn>1521-690X</isbn><urls></urls></record></Cite></EndNote>]. Individuals with thyroid conditions or iodine deficiencies are also expected to be at increased risk for adverse effects from perchlorate exposures [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>].

1.2 Evaluation of Perchlorate under the Safe Drinking Water Act

The EPA included perchlorate on the first three iterations of the Contaminant Candidate List (CCL), starting in 1998, after data collection and requests for comments. The CCL is a list of drinking water contaminants that are known or anticipated to occur in public water systems and are not currently subject to EPA drinking water regulations. Contaminants listed on the CCL may require future regulation under SDWA. The EPA uses the CCL to identify priority contaminants for regulatory decision making and information collection.

In 2005, at the request of the EPA and other federal agencies, the NRC evaluated the health implications of perchlorate ingestion. The NRC concluded that perchlorate exposure could inhibit the transport of iodide into the thyroid, leading to thyroid hormone deficiency [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>]. Significant inhibition of iodide uptake results in intra-thyroid iodide deficiency, decreased synthesis of key thyroid hormones (T3 and T4), and increased TSH. The NRC also concluded that a prolonged decrease of thyroid hormone is potentially more likely to have adverse effects in sensitive populations (e.g., people with thyroid disorders, pregnant women, fetuses, and infants). Based on the NRC's recommendations, the EPA adopted a reference dose (RfD) of 0.7 µg/kg/day in 2005 [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2005</Year><RecNum>295</RecNum><DisplayText>(U.S. EPA, 2005)</DisplayText><record><rec-number>295</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1470935048">295</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA, </author></authors><secondary-authors><author>National Center for Environmental Assessment</author></secondary-authors></contributors><titles><title>Integrated Risk Information System chemical assessment summary: Perchlorate and perchlorate salts</title></titles><dates><year>2005</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/1007_summary.pdf</style><style face="normal" font="default" size="100%"> </style></url></related-urls></urls></record></Cite></EndNote>]. This value was based on a no observed effect level of 7 µg/kg/day identified by a study [ADDIN EN.CITE <EndNote><Cite><Author>Greer</Author><Year>2002</Year><RecNum>204</RecNum><DisplayText>(Greer et al., 2002)</DisplayText><record><rec-number>204</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1467812686">204</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Greer, Monte A</author><author>Goodman,

Gay</author><author>Pleus, Richard C</author><author>Greer, Susan E</author></authors></contributors><titles><title>Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>927</pages><volume>110</volume><number>9</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] in healthy adults for inhibition of radioactive iodide uptake and the application of an uncertainty factor of 10 for intra-species variability.

In October 2008, the EPA published a preliminary determination not to regulate perchlorate in drinking water using a health reference level (HRL) of 15 µg/L, which was derived from the RfD of 0.7 µg/kg/day, using a default body weight (70 kg), a default drinking water consumption rate (2 L/day), and a perchlorate-specific relative source contribution (RSC) of 62% for a pregnant woman [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2008</Year><RecNum>121</RecNum><DisplayText>(U.S. EPA, 2008)</DisplayText><record><rec-number>121</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465916938">121</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Interim drinking water health advisory for perchlorate</title></titles><dates><year>2008</year></dates><pub-location>Washington, D.C.</pub-location><isbn>EPA 822-R-08-025</isbn><urls><related-urls><url><style face="underline" font="default" size="100%">https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1004X7Q.TXT</style></url></related-urls></urls></record></Cite></EndNote>]. The RSC is the percentage of the RfD remaining for drinking water after the other sources of exposure to perchlorate (e.g., food) have been considered. In December 2008, the EPA issued an interim health advisory (15 µg/L perchlorate in drinking water) to provide guidance to state and local officials in their efforts to address this issue. In August 2009, the EPA published a supplemental request for comment with a new analysis that derived potential alternative HRLs for 14 life stages, including infants and children. The analysis used the RfD of 0.7 µg/kg/day and life stage-specific body weight and exposure information (i.e., drinking water intake, RSC) [ADDIN EN.CITE <EndNote><Cite><Author>U.S. EPA</Author><Year>2008</Year><RecNum>121</RecNum><DisplayText>(U.S. EPA, 2008)</DisplayText><record><rec-number>121</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465916938">121</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Interim drinking water health advisory for perchlorate</title></titles><dates><year>2008</year></dates><pub-location>Washington, D.C.</pub-location><isbn>EPA 822-R-08-025</isbn><urls><related-urls><url><style face="underline" font="default" size="100%">https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1004X7Q.TXT</style></url></related-urls></urls></record></Cite></EndNote>]. The HRLs ranged from 1 µg/L to 47 µg/L.

After considering comments on the October 2008 and August 2009 notices, the EPA made a final determination to regulate perchlorate in drinking water in February 2011 [ADDIN EN.CITE

<EndNote><Cite><Author>U.S. EPA</Author><Year>2011</Year><RecNum>69</RecNum><DisplayText>(U.S. EPA, 2011)</DisplayText><record><rec-number>69</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1438181138">69</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Drinking water: regulatory determination on perchlorate. Federal Register Notice. 76 FR No. 29. Pages 7762-7767. (February 11, 2011) (to be codified at 40 C.F.R pt. 141).</title></titles><volume>2015</volume><number>July 29</number><dates><year>2011</year></dates><pub-location>Washington, D.C.</pub-location><urls><related-urls><url><style face="underline" font="default" size="100%">https://www.federalregister.gov/articles/2011/02/11/2011-2603/drinking-water-regulatory-determination-on-perchlorate</style></url></related-urls></urls></record></Cite></EndNote>]. As a result of the determination, the EPA initiated the process to develop an MCLG and National Primary Drinking Water Regulation for perchlorate under SDWA.

In accordance with SDWA, the Agency requested the EPA's Science Advisory Board (SAB) to provide recommendations for how to consider available data in deriving an MCLG for use in developing a National Primary Drinking Water Regulation for perchlorate. The EPA presented the SAB with a description of the general approach used by the Agency to derive an MCLG for non-carcinogenic chemicals. This approach relies on the following equation:

$$MCLG\ \left(\frac{\mu g}{L}\right) = \frac{RfD \times BW}{DWI} \times RSC$$

Where:

RfD = RfD of the contaminant (µg/kg/day); in the initial assessment for perchlorate, the EPA used NRC's recommended RfD of 0.7 µg/kg/day

BW = body weight (kg)

DWI = drinking water ingestion rate (L/day)

RSC = relative source contribution

The EPA also presented information to the SAB about life stage considerations, PBPK modeling, and epidemiologic and biomonitoring studies. The SAB released its final report on May 29, 2013, and recommended that the EPA "derive a perchlorate MCLG that addresses sensitive life stages through physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling based upon its mode of action rather than the default MCLG approach using the RfD and specific chemical exposure parameters" (SAB, 2013, p. 2). The SAB stated that this approach should follow perchlorate exposure through NIS inhibition to thyroid hormone change and finally to neurodevelopmental effects [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><DisplayText>(SAB, 2013)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government

Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>]. This framework would incorporate the endpoint of iodide uptake inhibition that was the basis for the RfD as part of this broader and more comprehensive framework that links perchlorate exposure to adverse neurodevelopmental outcomes.

In addition, the SAB stated that the EPA should more directly consider thyroid hormone changes as relevant to sensitive life stages; specifically, the fetus of hypothyroxinemic pregnant women and infants and neonates exposed to perchlorate through either water-based formula preparations or the breast milk of lactating women [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><DisplayText>(SAB, 2013)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>]. This is because thyroid hormone deficiency is known to produce adverse effects on human neurodevelopment, an effect to which the above-mentioned sensitive life stages are especially vulnerable. This direction is different from the conclusions of the NRC report, which based the RfD on the non-adverse effect of reduced iodide uptake and suggested examining pregnant women with hypothyroidism or iodide deficiency [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>]. The SAB approach focuses on the subtler changes in thyroid hormones (specifically fT4) associated with maternal hypothyroxinemia rather than broader changes in thyroid hormones (both fT4 and TSH) associated with hypothyroidism[]. Furthermore, the SAB recommended that the EPA consider available data on potential adverse health effects (i.e., neurodevelopmental outcomes) due to thyroid hormone level perturbations, regardless of the cause of those perturbations [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><DisplayText>(SAB, 2013)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-

authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>].

To address these recommendations, the EPA revised the existing biologically based dose-response (BBDR) and PBPK/PD models [ADDIN EN.CITE <EndNote><Cite><Author>Lumen</Author><Year>2013</Year><RecNum>107</RecNum><DisplayText>(Lumen, Mattie, & Fisher, 2013; U.S. EPA, 2009)</DisplayText><record><rec-number>107</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1450367396">107</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lumen, A.</author><author>Mattie, D.R.</author><author>Fisher, J.W.</author></authors></contributors><titles><title>Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model</title><secondary-title>Toxicological Sciences</secondary-title></titles><periodical><full-title>Toxicological Sciences</full-title></periodical><pages>320-341</pages><volume>133</volume><number>2</number><section>320</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1093/toxsci/kft078</electronic-resource-num></record></Cite><Cite><Author>U.S. EPA</Author><Year>2009</Year><RecNum>205</RecNum><record><rec-number>205</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1467814701">205</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>U.S. EPA,</author></authors></contributors><titles><title>Inhibition of the sodium-iodide symporter by perchlorate: an evaluation of lifestage sensitivity using physiologically based pharmacokinetic (PBPK) modeling (Final Report)</title></titles><dates><year>2009</year></dates><pub-location>Washington, D.C. </pub-location><isbn>EPA/600/R-08/106A</isbn><urls></urls></record></Cite></EndNote>] to create a BBDR model that predicts changes in thyroid hormone (i.e., T4, fT4, and T3) levels as a result of nutritional iodine intake and perchlorate exposure in women prior to pregnancy and early gestation. The EPA originally developed a set of BBDR models that included all sensitive life stages identified by the SAB (i.e., fetuses (by modeling a pregnant mother at 40 gestational weeks), neonates, and infants (SAB, 2013)) with the pregnancy model representing the third trimester. These models were peer reviewed in January 2017.[3] Reviewers stressed the importance of developing an early pregnancy model when considering adverse neurodevelopmental impacts. This was confirmed by the results of the EPA's literature review (summarized in Section [REF _Ref488161860 \n \h]), which found limited to no data regarding altered thyroid hormone levels and subsequent neurodevelopment effects on life stages other than early pregnancy. Therefore, the EPA responded to this peer review by developing an early pregnancy

[3] For a more detailed discussion on the development of the draft model, its calibration, and dose-response evaluations, please see the draft BBDR model report titled *Biologically Based Dose Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analysis.* The report is available through the docket at [HYPERLINK "http://www.regulations.gov"] *(Docket ID No. EPA-HQ-OW-2016-0439-0006).*

model and updated key parameters for that model. The models for the other sensitive life stages were not revised given the importance of early pregnancy thyroid hormones to offspring neurodevelopment [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Consequently, this report concentrates on fetuses of hypothyroxinemic women early in pregnancy as the sensitive life stage. The EPA carried out a subsequent peer review in January 2018 to evaluate updates to the BBDR model and presented the approaches that link the revised perchlorate BBDR model predictions to neurodevelopmental effects. The January 2018 peer review was largely supportive of the efforts described in the first draft of this document as evidenced by the following from the peer review final report:

> The panel commends EPA for the substantial amount of work done in creating the new modeling and preparing the report under review. It was highly responsive to the review comments from a year ago. Overall, the panel agreed that the EPA and its collaborators have prepared a highly innovative state-of-the-science set of quantitative tools to evaluate neurodevelopmental effects that could arise from drinking water exposure to perchlorate. While there is always room for improvement of the models, with limited additional work to address the committee's comments [in the peer review report], the current models are fit-for-purpose to determine an MCLG [ADDIN EN.CITE <EndNote><Cite><Author>External Peer Reviewers for U.S. EPA</Author><Year>2018</Year><RecNum>1974</RecNum><Pages>2</Pages><DisplayText>(EPA, 2018, p. 2)</DisplayText><record><rec-number>1974</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1521552479">1974</key></foreign-keys><ref-type name="Unpublished Work">34</ref-type><contributors><authors><author>External Peer Reviewers for U.S. EPA</author></authors><secondary-authors><author>Versar Inc. for U.S. EPA</author></secondary-authors></contributors><titles><title>External peer review for U.S. EPA's proposed approaches to inform the derivation of a maximum contaminant level goal for perchlorate in drinking water</title></titles><dates><year>2018</year></dates><urls></urls></record></Cite></EndNote>].

1.3 Objective of the Report

The purpose of this document is to present revisions made to the BBDR model and approaches that link the revised perchlorate BBDR model predictions to neurodevelopmental effects in response to the prior peer reviews. The document does not derive an MCLG; rather, it presents alternative approaches that might be used to inform future decisions including the derivation of an MCLG in accordance with SDWA (see [REF _Ref417634154 \h]).

Figure [SEQ Figure * ARABIC]. Summary of Modeling Approach for Estimating Measurable Adverse Neurodevelopmental Impacts in Pregnant Women Exposed to Perchlorate

[EMBED Visio.Drawing.15]

Section [REF _Ref516911407 \r \h] of the report describes how perchlorate can disrupt thyroid hormone homeostasis along with the common causes and consequences of such disruptions, including neurodevelopmental alterations following the proposed mode of action put forward by the NRC and modified by the SAB. Section [REF _Ref482972651 \r \h] of the report provides an overview of the EPA's BBDR model, and Section [REF _Ref482274870 \r \h] of the report describes how the BBDR model output relates to a distribution of thyroid hormone levels. The remainder of the report is focused on connecting the predicted changes in thyroid hormone levels from the BBDR model to downstream impacts, indicated as Step 2 in [REF _Ref417634154 \h * MERGEFORMAT].

Section [REF _Ref488161860 \n \h] provides details on the literature search and review process that led to the identification of studies to link the BBDR model outputs to quantitative alterations in neurodevelopmental endpoints. Section [REF _Ref456208917 \n \h * MERGEFORMAT] outlines an approach to utilize the identified studies to link the revised perchlorate BBDR model predictions to neurodevelopmental effects. Section [REF _Ref481160968 \r \h] includes a discussion on an alternative approach based on hypothyroxinemia. Section [REF _Ref488662930 \n \h] provides a short description of other potential adverse health impacts besides neurodevelopment that may be related to perchlorate exposure. Lastly, Section [REF _Ref456170011 \r \h] presents the main conclusions for this report.

2. Background on Thyroid Hormone Physiology and Connection to Neurodevelopment

In order to understand the approaches the EPA is considering to inform future decisions including the derivation of an MCLG in accordance with SDWA, it is first necessary to have a basic understanding of thyroid physiology (Section [REF _Ref427059872 \r \h]), including during pregnancy (Section [REF _Ref456164565 \r \h]), and pathophysiology (Section [REF _Ref486250699 \r \h]). It is also necessary to understand the mode of action by which perchlorate impacts thyroid hormone levels as put forward by the NRC [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>] and modified by the SAB [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>] (Section [REF _Ref427059909 \r \h]), how perchlorate is distributed and eliminated from the body (Section [REF _Ref459122801 \n \h]), and how thyroid hormones impact neurodevelopment (Section [REF _Ref427059920 \r \h]). Having this basic understanding of the mode of action through which perchlorate could impact thyroid hormone levels, and how thyroid hormones could in turn impact neurodevelopment, will provide a basis for understanding the approaches presented in this document.

2.1 Overview of Thyroid Physiology

The thyroid gland is part of a "self-regulating" loop referred to as the hypothalamic-pituitary-thyroid (HPT) axis ([REF _Ref454999548 \h]), which controls metabolism, growth, and brain development and function [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2007</Year><RecNum>186</RecNum><Prefix>for review see </Prefix><DisplayText>(for review see Zoeller, Tan, & Tyl, 2007)</DisplayText><record><rec-number>186</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202457">186</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Tan, Shirlee W</author><author>Tyl, Rochelle W</author></authors></contributors><titles><title>General background on the hypothalamic-

pituitary-thyroid (HPT) axis</title><secondary-title>Critical Reviews in Toxicology</secondary-title></titles><periodical><full-title>Critical reviews in toxicology</full-title></periodical><pages>11-53</pages><volume>37</volume><number>1-2</number><dates><year>2007</year></dates><isbn>1040-8444</isbn><urls></urls></record></Cite></EndNote>]. Low circulating levels of thyroid hormones stimulate hypothalamic secretion of thyrotropin-releasing hormone (TRH), which diffuses into the anterior pituitary gland and stimulates the endocrine cells within the anterior pituitary (thyrotropes) to release TSH into the circulatory system. TSH acts on the thyroid gland to stimulate iodine uptake to result in thyroid hormone production. Iodide is taken up from circulation by the NIS; serum iodide is transported into thyroid gland follicles for synthesis into the thyroid hormones T4 and to a lesser extent T3. Endocrine disruptors, such as perchlorate, could interfere with this process by directly inhibiting the uptake of iodide, thereby reducing the production of thyroid hormone.

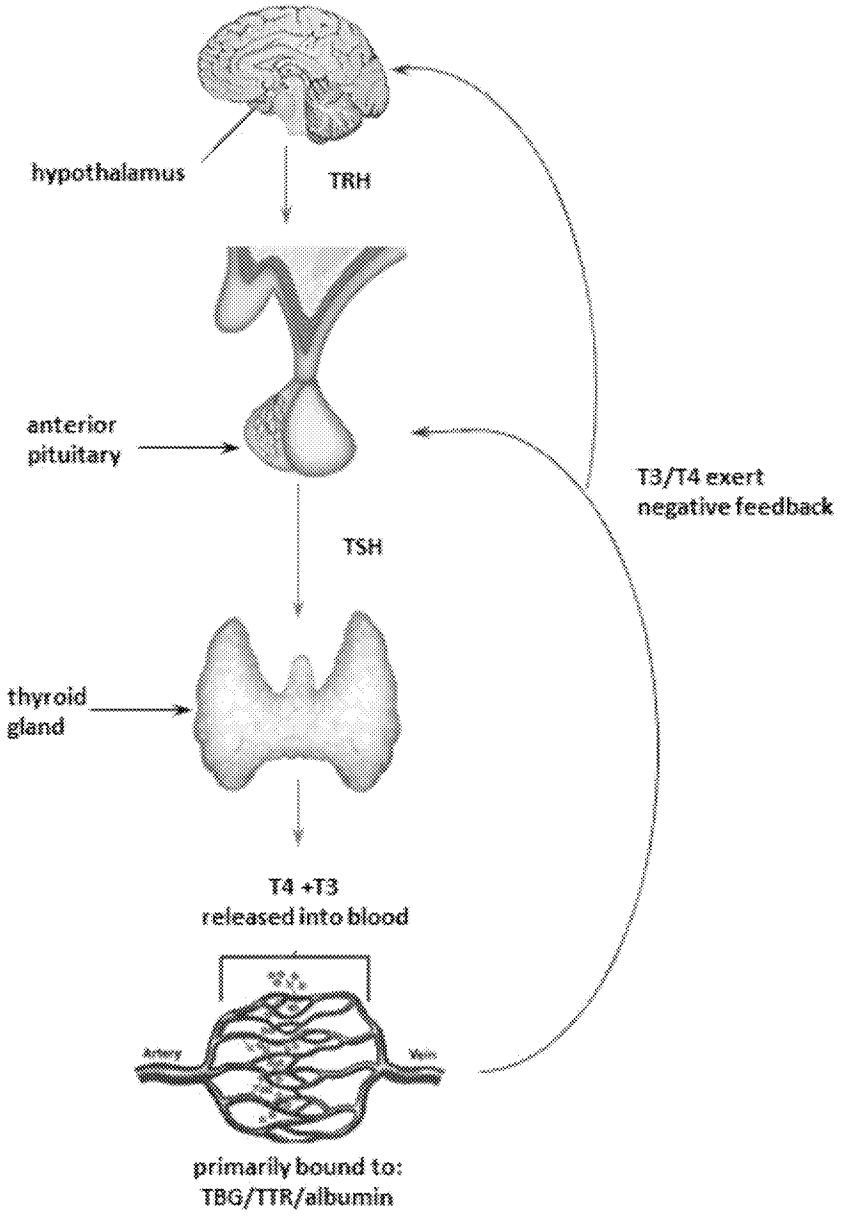
T3 and T4 are formed when thyroglobulin (Tg; the precursor protein of T3 and T4) produced by the thyroid follicular cells is iodinated by the enzyme thyroperoxidase, and the iodinated protein is cleaved. T4 is generally thought to act as the prohormone for the more biologically active T3, which is required for normal development of the central nervous system in fetuses and in infants, as well as for ultimate skeletal development and growth. However, it should be noted that the regulatory factors that modulate the delivery of T4 to the fetus are not fully understood. Both T3 and T4 are critical determinants of metabolic function in humans of all ages. T4 and T3 are released into circulation, where they are primarily bound to the carrier proteins thyroxine-binding globulin (TBG), transthyretin (TTR), albumin, and lipoproteins [ADDIN EN.CITE ADDIN EN.CITE.DATA].

T3 and T4 in the blood that are bound to these proteins act largely as reserves because they are less readily metabolized in the liver and cannot enter cells unless in free form [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2007</Year><RecNum>186</RecNum><DisplayText>(Zoeller et al., 2007)</DisplayText><record><rec-number>186</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202457">186</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Tan, Shirlee W</author><author>Tyl, Rochelle W</author></authors></contributors><titles><title>General background on the hypothalamic-pituitary-thyroid (HPT) axis</title><secondary-title>Critical Reviews in Toxicology</secondary-title></titles><periodical><full-title>Critical reviews in toxicology</full-title></periodical><pages>11-53</pages><volume>37</volume><number>1-2</number><dates><year>2007</year></dates><isbn>1040-8444</isbn><urls></urls></record></Cite></EndNote>]. However, in their free (or unbound) states (the free or unbound states of T4 and T3 are denoted as fT4 and fT3), both are available to be transported actively into specific cells. T4 is transported through the cellular membrane by specific transporters and transformed by deiodinases into T3, which is then transferred to the nucleus to cause transcriptional changes. Circulating T3 is mostly derived from peripheral monodeionization of T4 [ADDIN EN.CITE <EndNote><Cite><Author>Chanoine</Author><Year>1993</Year><RecNum>343</RecNum><DisplayText>(Chanoine, Braverman, & Farwell, 1993; Peeters & Visser, 2017)</DisplayText><record><rec-number>343</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495028650">343</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chanoine, J.P. </author><author>Braverman, L.E. </author><author>Farwell, A.P.

</author></authors></contributors><titles><title>The thyroid gland is a major source of circulating T3 in the rat</title><secondary-title>Journal of Clinical Investigation</secondary-title></titles><periodical><full-title>Journal of Clinical Investigation</full-title></periodical><pages>2709-2713</pages><volume>91</volume><number>6</number><dates><year>1993</year></dates><urls></urls></record></Cite><Cite><Author>Peeters</Author><Year>2017</Year><RecNum>344</RecNum><record><rec-number>344</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495029973">344</key></foreign-keys><ref-type name="Electronic Book">44</ref-type><contributors><authors><author>Peeters, R.</author><author>Visser, T.</author></authors><secondary-authors><author>De Groot, LJ</author><author>Chrousos, G </author><author>Dungan, K </author><author>et al.</author></secondary-authors></contributors><titles><title>Metabolism of thyroid hormone</title></titles><dates><year>2017</year></dates><publisher>Endotext (Internet)</publisher><urls><related-urls><url><style face="underline" font="default" size="100%">https://www.ncbi.nlm.nih.gov/books/NBK285545/</style></url></related-urls></urls></record></Cite></EndNote>]. Circulating T3 and T4 levels in an individual are maintained within a narrow range by a negative feedback loop with TSH from the pituitary and TRH from the hypothalamus (see [REF _Ref454999548 \h]) that operates around a "set point." This set point is different from individual to individual, which generates a population variance in blood levels of thyroid hormone that is considerably broader than the individual variance [ADDIN EN.CITE <EndNote><Cite><Author>Andersen</Author><Year>2002</Year><RecNum>333</RecNum><DisplayText>(S. Andersen, Pedersen, Bruun, & Laurberg, 2002)</DisplayText><record><rec-number>333</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1494274249">333</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Andersen, S.</author><author>Pedersen, K.M.</author><author>Bruun, N.H.</author><author>Laurberg, P.</author></authors></contributors><titles><title>Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1068-1072</pages><volume>87</volume><number>3</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>]. Therefore, in euthyroid individuals, serum T4 and T3 fluctuate within a fairly narrow range (about 10% of the population variance), maintained by the negative feedback relationship with serum TSH from the pituitary gland. This normal variation creates a situation where single measures of free or total T4 and TSH are a somewhat imprecise measure of an individual's average T4 and TSH concentrations [ADDIN EN.CITE <EndNote><Cite><Author>Andersen</Author><Year>2002</Year><RecNum>333</RecNum><DisplayText>(S. Andersen et al., 2002)</DisplayText><record><rec-number>333</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1494274249">333</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Andersen, S.</author><author>Pedersen, K.M.</author><author>Bruun, N.H.</author><author>Laurberg, P.</author></authors></contributors><titles><title>Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1068-

1072</pages><volume>87</volume><number>3</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>].

Figure [SEQ Figure * ARABIC]. Summary of HPT Axis Showing Negative Feedback of Increased Circulating T4 and T3 on Hypothalamus and Anterior Pituitary



It is generally thought that changes in thyroid hormone levels that occur during pregnancy operate independently of changes in the set point. For example, as the first trimester progresses, increases in

human chorionic gonadotropin (hCG),[4] estrogen, and thyroxine-binding protein result in a higher blood concentration of total T4, making more fT4 available to the developing fetus [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2007</Year><RecNum>201</RecNum><DisplayText>(G Morreale de Escobar, Obregón, & Escobar del Rey, 2007)</DisplayText><record><rec-number>201</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466438813">201</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, María Jesús</author><author>Escobar del Rey, F. </author></authors></contributors><titles><title>Iodine deficiency and brain development in the first half of pregnancy</title><secondary-title>Public Health Nutrition</secondary-title></titles><periodical><full-title>Public health nutrition</full-title></periodical><pages>1554-1570</pages><volume>10</volume><number>12A</number><dates><year>2007</year></dates><isbn>1475-2727</isbn><urls></urls></record></Cite></EndNote>]. Serum TSH concentrations are also mildly suppressed due to the negative feedback of this elevated serum T4 on TSH.

2.2 Thyroid Physiology in Pregnancy

In general, pregnancy requires the maternal thyroid gland to increase thyroid hormone production by around 50% [ADDIN EN.CITE <EndNote><Cite><Author>Skeaff</Author><Year>2011</Year><RecNum>180</RecNum><Prefix>for review see </Prefix><DisplayText>(for review see Skeaff, 2011)</DisplayText><record><rec-number>180</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466200929">180</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Skeaff, Sheila A</author></authors></contributors><titles><title>Iodine deficiency in pregnancy: the effect on neurodevelopment in the child</title><secondary-title>Nutrients</secondary-title></titles><periodical><full-title>Nutrients</full-title></periodical><pages>265-273</pages><volume>3</volume><number>2</number><dates><year>2011</year></dates><urls></urls></record></Cite></EndNote>] in order to provide sufficient fT4 for fetal brain development. In the first trimester of pregnancy, this increased output of thyroid hormones is, in part, due to estrogen increases during the first trimester, which increases the serum concentration of TBG, one of the main proteins to which T4 binds. The combination of increased TBG and hCG results in an increase in total T4 of about 50% over the pre-pregnancy level [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><

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[4] hCG is a hormone produced during pregnancy by cells in the placenta [ADDIN EN.CITE <EndNote><Cite><Author>American Pregnancy Association</Author><Year>2016</Year><RecNum>206</RecNum><DisplayText>(American Pregnancy Association, 2016)</DisplayText><record><rec-number>206</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1467819649">206</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>American Pregnancy Association,</author></authors></contributors><titles><title>Human chorionic gonadotropin (HCG): The pregnancy hormone</title></titles><dates><year>2016</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">http://americanpregnancy.org/while-pregnant/hcg-levels/</style></url></related-urls></urls></record></Cite></EndNote>].

DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. This increase in serum total T4 also increases serum fT4 during the first trimester, although fT4 levels fall over the next two trimesters [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. The first-trimester increase in fT4 can lead in turn to a lower TSH concentration compared to the pre-pregnancy state.

Given the increased demand on the maternal thyroid in pregnancy, there is an increased demand for iodine to support additional hormone synthesis. If the maternal thyroid is fully functional, then sufficient dietary iodine intake will enable this to occur. According to the SAB, maternal hypothyroxinemia has been defined by a "variety of cutoffs…ranging from fT4 below the 10th or 5th percentiles to below the 2.5th percentile" [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Pages>10</Pages><DisplayText>(SAB, 2013, p. 10)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>] in the population. Although a fully functional system (i.e., in euthyroid individuals) can compensate with additional iodine consumption, hypothyroxinemic individuals are already compromised, and iodine insufficiency can exacerbate this situation, putting the fetus at risk of neurological deficits [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Maternal fT4 is particularly important in the first trimester of pregnancy because the fetal brain is solely dependent upon T4 of maternal origin during this period

[ADDIN EN.CITE
<EndNote><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><DisplayText>(Zoeller & Rovet, 2004)</DisplayText><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet, J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>], as the fetal thyroid gland is not formed until later in development. Low maternal iodine may also impair fetal thyroid function once it begins, thereby putting the fetus at risk of developing hypothyroxinemia because it does not have enough iodine with which to synthesize its own thyroid hormone(s) ([HYPERLINK \l "_ENREF_32" \o "Dosiou, 2017 #325"]).

2.3 Thyroid Pathophysiology

Historically, the most commonly observed thyroid conditions have been goiter (i.e., enlarged thyroid gland) and congenital hypothyroidism. Hypothyroidism is defined as serum fT4 below and serum TSH above the reference range. Hypothyroidism may result from iodine insufficiency, from genetic disorders, autoimmune disease, cancer, pituitary insufficiency, or environmental factors. The most common form of adult hypothyroidism results from an autoimmune thyroiditis (Hashimoto's disease) whereby a variety of cellular and antibody-related immune processes reduce thyroid hormone production within the gland [ADDIN EN.CITE
<EndNote><Cite><Author>Pyzik</Author><Year>2015</Year><RecNum>198</RecNum><Prefix>for review see </Prefix><DisplayText>(for review see Pyzik, Grywalska, Matyjaszek-Matuszek, & Roliński, 2015)</DisplayText><record><rec-number>198</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466427626">198</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pyzik, Aleksandra</author><author>Grywalska, Ewelina</author><author>Matyjaszek-Matuszek, Beata</author><author>Roliński, Jacek</author></authors></contributors><titles><title>Immune disorders in Hashimoto's Thyroiditis: What do we know so far?</title><secondary-title>Journal of Immunology Research</secondary-title></titles><periodical><full-title>Journal of immunology research</full-title></periodical><volume>2015</volume><dates><year>2015</year></dates><isbn>2314-8861</isbn><urls></urls></record></Cite></EndNote>]. Both post-partum thyroiditis and subacute lymphocytic (or silent) thyroiditis are considered subtypes of this disorder. Post-partum thyroiditis can occur in up to 5% of women and can involve periods of hyper- and hypo-thyroid activity [ADDIN EN.CITE
<EndNote><Cite><Author>Akamizu</Author><Year>2015</Year><RecNum>169</RecNum><Prefix>for review see </Prefix><DisplayText>(for review see Akamizu & Amino, 2015; Pearce, 2015b)</DisplayText><record><rec-number>169</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466199550">169</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Akamizu, T.</author><author>Amino, N.</author></authors><secondary-authors><author>De Groot,

L.J.</author><author>Chrouos, G.</author><author>Dungan, K.</author><author>Feingold, K.R.</author><author>Grossman, A.</author><author>Hershman, J.M.</author><author>Koch, C. </author><author>Korbonits, M.</author><author>McLachlan, R. </author><author>New, M. </author><author>Purnell, J.</author><author>Rebar, R. </author><author>Singer, F. </author><author>Vinik, A. </author></secondary-authors></contributors><titles><title>Hashimoto's Thyroiditis</title><secondary-title>Endotext </secondary-title></titles><dates><year>2015</year></dates><pub-location>South Dartmouth, MA</pub-location><publisher>MDText.com, Inc.</publisher><urls></urls></record></Cite><Cite><Author>Pearce</Author><Year>2015</Year><RecNum>179</RecNum><record><rec-number>179</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466200902">179</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pearce, E.N.</author></authors></contributors><titles><title>Thyroid disorders during pregnancy and postpartum</title><secondary-title>Best Practice & Research Clinical Obstetrics & Gynaecology</secondary-title></titles><periodical><full-title>Best Practice & Research Clinical Obstetrics & Gynaecology</full-title></periodical><pages>700-706</pages><volume>29</volume><number>5</number><dates><year>2015</year></dates><isbn>1521-6934</isbn><urls></urls></record></Cite></EndNote>]. Generally, the condition will resolve itself; however, as many as 20% of cases may lead to permanent hypothyroidism.

Hashimoto's disease increases the risk of hypothyroidism, including both subclinical and overt hypothyroidism. Subclinical hypothyroidism is defined by only elevated (or outside the reference range) TSH concentrations, with serum T3 and T4 concentrations that remain within the population reference range, while overt hypothyroidism is defined by elevated serum TSH concentrations concurrent with decreased (or outside the reference range) serum T3 and T4 concentrations. Subclinical hypothyroidism has the potential to progress to overt hypothyroidism over time; thus, it requires serum thyroid function test monitoring. Other related autoimmune hypothyroid conditions include primary thyroid atrophy (Ord's disease), which is characterized by thyroid atrophy through invasion by T-lymphocytes, and is likely part of the continuum of hypothyroid conditions, rather than a separate disorder from Hashimoto's disease [ADDIN EN.CITE <EndNote><Cite><Author>Carlé</Author><Year>2009</Year><RecNum>172</RecNum><DisplayText>(Carlé et al., 2009)</DisplayText><record><rec-number>172</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466200413">172</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Carlé, Allan</author><author>Pedersen, Inge Bulow</author><author>Knudsen, Nils</author><author>Perrild, Hans</author><author>Ovesen, Lars</author><author>Jørgensen, Torben</author><author>Laurberg, Peter</author></authors></contributors><titles><title>Thyroid volume in hypothyroidism due to autoimmune disease follows a unimodal distribution: evidence against primary thyroid atrophy and autoimmune thyroiditis being distinct diseases</title><secondary-title>The Journal of Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>The Journal of Clinical Endocrinology & Metabolism</full-title></periodical><pages>833-839</pages><volume>94</volume><number>3</number><dates><year>2009</year></dates><isbn>0021-972X</isbn><urls></urls></record></Cite></EndNote>]. Viral or other infections can result in the painful condition of subacute granulomatous thyroiditis. This condition, like post-partum thyroiditis, is generally transient and requires only beta-blocker and non-steroidal anti-inflammatory

drugs (NSAIDs) or steroid treatment to resolve. Although not common, pituitary disorders or tumors can also result in reduced thyroid function through reduction in TSH output.

Thyroid peroxidase antibodies (also referred to as anti-thyroid peroxidase antibodies or TPO Abs) are a marker for thyroid autoimmunity, a condition in which a person's immune system antibodies mistakenly target parts of the thyroid gland or thyroid proteins. Thyroid autoimmunity leads to chronic inflammation of the thyroid, can cause tissue damage, and may disrupt thyroid function. The TPO Abs work against thyroid peroxidase, which is an enzyme involved in the synthesis of thyroid hormones [ADDIN EN.CITE <EndNote><Cite><Author>Braverman</Author><Year>2004</Year><RecNum>1991</RecNum><DisplayText>(L Braverman & Utiger, 2004)</DisplayText><record><rec-number>1991</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1525112324">1991</key></foreign-keys><ref-type name="Book Section">5</ref-type><contributors><authors><author>Braverman, L </author><author>Utiger, R.S.</author></authors><secondary-authors><author>Taurog, A.</author></secondary-authors></contributors><titles><title>Hormone synthesis: Thyroid iodine metabolism.</title><secondary-title>The Thyroid: A Fundamental and Clinical Text.</secondary-title></titles><pages>61-85</pages><dates><year>2004</year></dates><pub-location>Philadelphia</pub-location><publisher>Lippincott-Raven</publisher><urls></urls></record></Cite></EndNote>].

2.4 Perchlorate's Impact on Thyroid Physiology

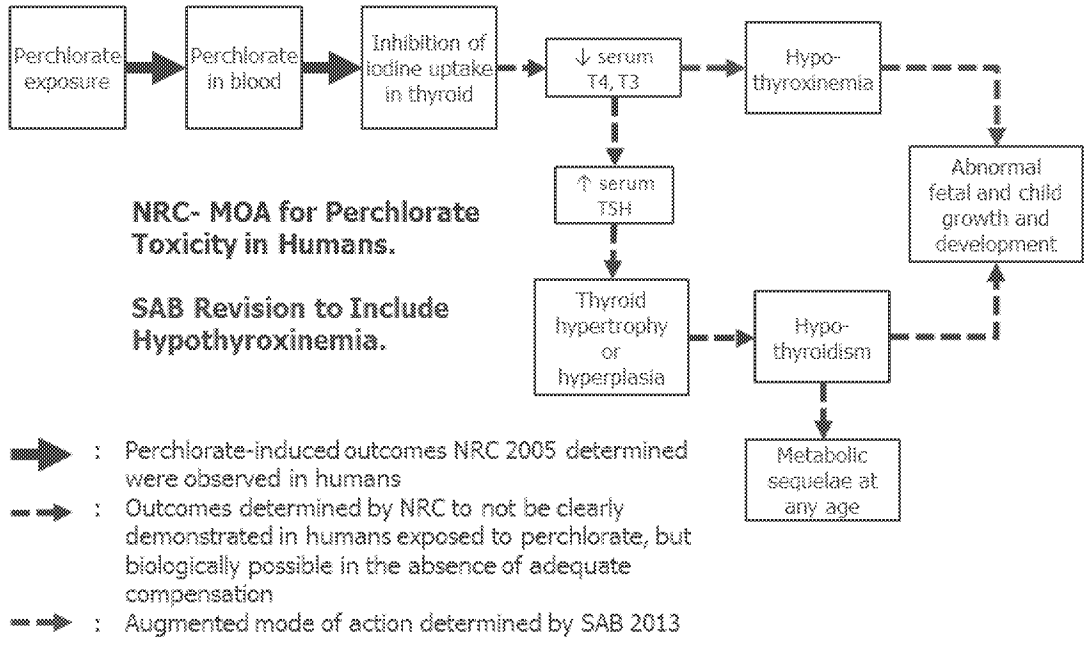
The NRC (2005) proposed a mode of action for perchlorate. [REF _Ref455000569 \h] is a reproduction of this mode of action modified to include hypothyroxinemia. Evaluating hypothyroxinemia as a result of perchlorate exposure is the mode of action that the SAB recommended the EPA utilize in evaluating the MCLG for perchlorate. [REF _Ref455000569 \h] begins with exposure to perchlorate, which then leads to perchlorate in the bloodstream, followed by the inhibition of iodide uptake in the thyroid. The NRC concluded that these steps have all been observed in humans, and any subsequent steps or results are biologically possible, but have not been clearly demonstrated in humans. However, since the 2005 NRC report was published, several epidemiological studies have shown perchlorate exposure to be associated with changes in serum thyroid hormone levels [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Furthermore, Taylor et al. (2014) demonstrated an association between high maternal perchlorate exposure and risk of low IQ in offspring.

In their review, NRC deemed the inhibition of iodide uptake in the thyroid to be a non-adverse effect, and concluded that the body's compensatory mechanisms would keep thyroid hormone levels within the population reference range [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-

date>National Research Council</modified-date></record></Cite></EndNote>]. However, concerns have been raised regarding this conclusion given the lack of empirical evidence provided to support it [ADDIN EN.CITE <EndNote><Cite><Author>Ginsberg</Author><Year>2007</Year><RecNum>345</RecNum><DisplayText>(Ginsberg, Hattis, Zoeller, & Rice, 2007)</DisplayText><record><rec-number>345</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495122121">345</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ginsberg, G.</author><author>Hattis, R.</author><author>Zoeller, R Thomas</author><author>Rice, D.C.</author></authors></contributors><titles><title>Evaluation of the U.S. EPA/OSWER Preliminary Remediation Goal for Perchlorate in Groundwater: Focus on Exposure to Nursing Infants</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><volume>115</volume><number>3</number><section>361</section><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>]. The NRC did list subsequent biologically plausible steps that include the following: altered thyroid hormone levels (e.g., decreased T3 and T4, increased TSH; which has now been demonstrated in the epidemiologic literature), growth of the thyroid gland (e.g., thyroid hypertrophy and hyperplasia), and hypothyroidism (defined above). Hypothyroidism, deemed by the NRC to be the first adverse effect, could lead to abnormal fetal and child growth development, as well as metabolic disorders at all ages. Given the importance of a properly functioning thyroid for fetal and child growth [ADDIN EN.CITE <EndNote><Cite><Author>Forhead</Author><Year>2014</Year><RecNum>1890</RecNum><DisplayText>(Forhead & Fowden, 2014)</DisplayText><record><rec-number>1890</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497623515">1890</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Forhead, A J</author><author>Fowden, A L</author></authors></contributors><titles><title>Thyroid hormones in fetal growth and prepartum maturation</title><secondary-title>Journal of Endocrinology</secondary-title></titles><periodical><full-title>Journal of Endocrinology</full-title></periodical><pages>R87-R103</pages><volume>221</volume><number>3</number><dates><year>2014</year><pub-dates><date>June 1, 2014</date></pub-dates></dates><urls><related-urls><url>http://joe.endocrinology-journals.org/content/221/3/R87.abstract</url></related-urls></urls><electronic-resource-num>10.1530/joe-14-0025</electronic-resource-num></record></Cite></EndNote>], both hypothyroidism and hypothyroxinemia may also be associated with abnormal fetal and child growth.

In the SAB report on approaches to derive an MCLG for perchlorate, the SAB indicates that "the mode of action of perchlorate toxicity is well understood" (SAB, 2013, p. 2). The SAB finds that "hypothyroxinemia (i.e., low levels of thyroid hormone) is a more appropriate indicator of the potential adverse health effects than the more pronounced decreases in thyroid hormone associated with hypothyroidism" (SAB, 2013, p. 2). Moreover, the "sensitive populations EPA should consider for exposure to perchlorate are the fetuses of hypothyroxinemic pregnant women" (SAB, 2013, p. 2). Thus, this report is following the SAB's recommendations.

Figure [SEQ Figure * ARABIC]. Modified Representation of NRC's Suggested Mode of Action for Perchlorate Toxicity in Humans Indicating First Adverse Effect in the Continuum of Perchlorate Exposure to Effect, Revised to Include Hypothyroxinemia as recommended by the SAB



Source: Adapted from NRC [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>National Research Council</Author><Year>2005</Year><RecNum>116</RecNum><Suffix>`, Figure 5-2 (modified)</Suffix><DisplayText>(2005, Figure 5-2 (modified))</DisplayText><record><rec-number>116</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914312">116</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>National Research Council (NRC),</author></authors></contributors><titles><title>Health implications of perchlorate exposure</title></titles><dates><year>2005</year></dates><pub-location>Washington, D.C.</pub-location><publisher>The National Academies Press</publisher><urls></urls></record></Cite></EndNote>].
Notes: Solid arrows represent outcomes that the NRC (2005) determined were observed in humans during perchlorate exposure. Black dashed arrows represent outcomes determined by the NRC (2005) to have not been clearly demonstrated in humans exposed to perchlorate, but that are biologically possible in the absence of adequate compensation. Blue dashed arrows represent the augmented mode of action from the SAB.

In addition to the NRC's proposed mode of action for perchlorate, it is also important to note that the interruption of iodide uptake by perchlorate creates a deficit that can accentuate the effect of other goitrogenic (i.e., goiter-causing) anions on the symporter. For example, [HYPERLINK \l "_ENREF_107" \o "Steinmaus, 2007 #199"] [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Steinmaus</Author><Year>2007</Year><RecNum>199</RecNum><DisplayText>(2007)</DisplayText><record><rec-number>199</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466428909">199</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Steinmaus, C</author><author>Miller, Mark D</author><author>Howd, Robert</author></authors></contributors><titles><title>Impact of smoking and thiocyanate on perchlorate and thyroid hormone associations in the 2001-2002 National Health and Nutrition Examination Survey</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health

Perspectives</full-title></periodical><pages>1333-1338</pages><dates><year>2007</year></dates><isbn>0091-6765</isbn><urls></urls></record></Cite><Cite><Author>Steinmaus</Author><Year>2007</Year><RecNum>199</RecNum><record><rec-number>199</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466428909">199</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Steinmaus, C</author><author>Miller, Mark D</author><author>Howd, Robert</author></authors></contributors><titles><title>Impact of smoking and thiocyanate on perchlorate and thyroid hormone associations in the 2001-2002 National Health and Nutrition Examination Survey</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>1333-1338</pages><dates><year>2007</year></dates><isbn>0091-6765</isbn><urls></urls></record></Cite></EndNote>] demonstrated that the combined effect of smoking and perchlorate is much greater than the effect of perchlorate or smoking on its own. Smoking cigarettes greatly increases an individual's exposure to thiocyanate, a known goitrogen. Thus, this upstream effect creates a vulnerability that increases the potential for chemical–chemical interaction (e.g., between perchlorate and other goitrogenic anions; or, between perchlorate and other anti-thyroid agents, such as polychlorinated biphenyls (PCBs)). It also increases the potential for chemical–nutritive status interaction (e.g., between perchlorate and low iodine intake), and perchlorate–physiological status interaction (e.g., between pregnancy, neonatal adaptation, aging, and disease status) in which the functional reserve of the HPT system is limited.

While perchlorate is expected to impair the production of T4 by the thyroid gland by competitively inhibiting the transfer of iodide into the thyroid gland, other environmental contaminants have been implicated as endocrine disruptors of other components of the HPT axis or plasma transport proteins. Multiple other chemicals, such as PCBs, polybrominated diphenyl ethers (PBDEs), bisphenol A, and perfluorinated acids (PFAs), also disrupt thyroid homeostasis [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These disruptions occur through various mechanisms of action including directly affecting the thyroid's responsiveness to TSH [ADDIN EN.CITE <EndNote><Cite><Author>Bansal</Author><Year>2008</Year><RecNum>170</RecNum><DisplayText>(Bansal & Zoeller, 2008)</DisplayText><record><rec-number>170</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466200263">170</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Bansal, Ruby</author><author>Zoeller, R Thomas</author></authors></contributors><titles><title>Polychlorinated biphenyls (Aroclor 1254) do not uniformly produce agonist actions on thyroid hormone responses in the developing rat brain</title><secondary-title>Endocrinology</secondary-title></titles><periodical><full-title>Endocrinology</full-title></periodical><pages>4001-4008</pages><volume>149</volume><number>8</number><dates><year>2008</year></dates><isbn>0013-7227</isbn><urls></urls></record></Cite></EndNote>], affecting binding proteins [ADDIN EN.CITE ADDIN EN.CITE.DATA], preventing NIS-mediated iodide uptake, and affecting expression of thyroid hormone-producing genes [ADDIN EN.CITE <EndNote><Cite><Author>Wu</Author><Year>2016</Year><RecNum>183</RecNum><DisplayText>(Wu, Beland, & Fang, 2016)</DisplayText><record><rec-number>183</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466201102">183</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Wu, Yuanfeng</author><author>Beland, Frederick A</author><author>Fang, Jia-Long</author></authors></contributors><titles><title>Effect of triclosan, triclocarban, 2, 2′, 4, 4′-tetrabromodiphenyl ether, and bisphenol A on the iodide uptake, thyroid peroxidase activity, and expression of genes involved in thyroid hormone synthesis</title><secondary-title>Toxicology in Vitro</secondary-title></titles><periodical><full-title>Toxicology in Vitro</full-title></periodical><pages>310-319</pages><volume>32</volume><dates><year>2016</year></dates><isbn>0887-2333</isbn><urls></urls></record></Cite></EndNote>]. Bioaccumulation and co-exposures of persistent environmental contaminants can result in populations with high body burdens of contaminants that vary substantially with diet, region, gender, age, and body mass index (BMI). Even without the presence of perchlorate as a thyroid disruptor, it is likely that the population is already exposed to a range of thyroid-affecting substances that may result in overt hypothyroidism (elevated TSH, low fT4), subclinical hypothyroidism (elevated TSH, normal fT4), or hypothyroxinemia (normal TSH, low fT4) that will effectively be worsened by exposure to further endocrine disruption caused by perchlorate.

2.5 Distribution and Excretion of Perchlorate

Perchlorate salts such as ammonium, potassium, or sodium are highly water soluble and readily ionize in water. Once ingested, perchlorate is rapidly absorbed by the gastrointestinal tract and passed into circulation. In single-dose studies perchlorate has a short half-life of only 5–12 hours, but may be measured in urine within as little as 10 minutes to 3 hours after ingestion [ADDIN EN.CITE <EndNote><Cite><Author>Anbar</Author><Year>1959</Year><RecNum>264</RecNum><DisplayText>(Anbar, Guttmann, & Lewitus, 1959)</DisplayText><record><rec-number>264</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468519973">264</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Anbar, M.</author><author>Guttmann, S.</author><author>Lewitus, Z.</author></authors></contributors><titles><title>The mode of action of perchlorate ions on the iodine uptake of the thyroid gland</title><secondary-title>International Journal of Applied Radiation and Isotopes</secondary-title></titles><periodical><full-title>International Journal of Applied Radiation and Isotopes</full-title></periodical><pages>87-96</pages><volume>7</volume><edition>1959/12/01</edition><keywords><keyword>Iodine/*metabolism</keyword><keyword>Perchloric Acid/*pharmacology</keyword><keyword>Thyroid Gland/*pharmacology</keyword></keywords><dates><year>1959</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>0020-708X (Print)
0020-708X (Linking)</isbn><accession-num>13793274</accession-num><urls><related-urls><url><style face="underline" font="default" size="100%">http://www.ncbi.nlm.nih.gov/pubmed/13793274</style></url></related-urls></urls><research-notes><style face="bold" font="default" size="100%">Abt to Include</style></research-notes><language>eng</language></record></Cite></EndNote>]. Short-duration (2-week exposure) studies indicate a half-life of approximately 8 hours [ADDIN EN.CITE <EndNote><Cite><Author>Greer</Author><Year>2002</Year><RecNum>204</RecNum><DisplayText>(Greer et al., 2002)</DisplayText><record><rec-number>204</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1467812686">204</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Greer, Monte A</author><author>Goodman,

Gay</author><author>Pleus, Richard C</author><author>Greer, Susan E</author></authors></contributors><titles><title>Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>927</pages><volume>110</volume><number>9</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>], with as much as 77% of the perchlorate being excreted per day with consumption of 0.14 mg/kg/day [ADDIN EN.CITE <EndNote><Cite><Author>Lawrence</Author><Year>2000</Year><RecNum>228</RecNum><DisplayText>(Lawrence et al., 2000)</DisplayText><record><rec-number>228</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468246590">228</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lawrence, J.E.</author><author>S.H. Lamm</author><author>S. Pino</author><author>K. Richman</author><author>Braverman, L</author></authors></contributors><titles><title>The effect of short-term low-dose perchlorate on various aspects of thyroid function</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>659-663</pages><volume>10</volume><number>8</number><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>]. A six-month low-dose study of healthy volunteers at 0.5 mg or 3.0 mg per day indicated daily excretion rates of 0.3 $\pm$ 0.07 mg/day and 2.1 $\pm$ 0.43 mg/day, respectively [ADDIN EN.CITE <EndNote><Cite><Author>Braverman</Author><Year>2006</Year><RecNum>225</RecNum><DisplayText>(L Braverman et al., 2006)</DisplayText><record><rec-number>225</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468246163">225</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Braverman, L</author><author>Pearce, E.N.</author><author>He, X.</author><author>Pino, S.</author><author>Seeley, M.</author><author>Beck, B.</author><author>Magnani, B.</author><author>Bleunt, B.C.</author><author>Firek, A.</author></authors></contributors><titles><title>Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2721-94</pages><volume>91</volume><number>7</number><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>], representing approximately 60% and 70% excretion of perchlorate per day. There is little to no metabolic conversion or catabolism of perchlorate ions prior to excretion.

The remaining perchlorate is transported by the NIS in the thyroid, kidney, gastric mucosa, salivary glands, placenta, mammary glands, and choroid plexus [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Placental NIS plays a role in ensuring adequate transfer of maternal iodide to the fetus by actively transferring iodide from the maternal blood circulation to the fetal blood circulation. Disruption of the supply processes, either due to low maternal T3/T4 levels, or by inhibition of the placental NIS by perchlorate, may further reduce fetal T3/T4 levels. Competitive inhibition of placental NIS by perchlorate could reduce uptake of iodide from the maternal circulation and reduce thyroid hormone production within the fetal thyroid gland. Further, once the fetus has a

functional thyroid, inhibition of the fetal thyroidal NIS, as well as iodide deficiency from the blockade of the placental NIS, could result in additional reductions in fetal T3/T4 levels.

There is evidence from *in vivo* studies, confirmed by cell culture work, showing that perchlorate is actively transported into the thyroid gland and this transport may be enhanced by increasing TSH and reduced in a dose-dependent manner by iodide [ADDIN EN.CITE ADDIN EN.CITE.DATA]. This active transport is potentially due to the upregulation of NIS [ADDIN EN.CITE <EndNote><Cite><Author>Hussein</Author><Year>2012</Year><RecNum>303</RecNum><DisplayText>(Hussein, Abbas, El Wakil, Elsamanoudy, & El Aziz, 2012)</DisplayText><record><rec-number>303</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1471880522">303</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hussein, Abd El-Aziz M.</author><author>Abbas, Amr M.</author><author>El Wakil, Gehan A.</author><author>Elsamanoudy, Ayman Z.</author><author>El Aziz, Azza Abd</author></authors></contributors><titles><title>Effect of chronic excess iodine intake on thyroid function and oxidative stress in hypothyroid rats</title><secondary-title>Canadian Journal of Physiology and Pharmacology</secondary-title></titles><periodical><full-title>Canadian Journal of Physiology and Pharmacology</full-title></periodical><pages>617-625</pages><volume>90</volume><number>5</number><dates><year>2012</year><pub-dates><date>2012/05/01</date></pub-dates></dates><publisher>NRC Research Press</publisher><isbn>0008-4212</isbn><urls><related-urls><url>http://dx.doi.org/10.1139/y2012-046</url></related-urls></urls><electronic-resource-num>10.1139/y2012-046</electronic-resource-num><access-date>2016/08/22</access-date></record></Cite></EndNote>]. These observations have implications for the placental transfer of iodide and perchlorate and subsequent fetal thyroid functions. As yet there is no direct evidence to indicate that the quantity of placental NIS is upregulated in response to increased TSH in the same way, or to the same extent, as seen in Tran et al. (2008). However, if this is the case, additional stimulation by maternal TSH in the presence of perchlorate may result in an absolute increase in NIS and subsequently increase perchlorate transfer to the placenta. The immature fetal HPT axis has very limited capacity to increase output of thyroid hormones [ADDIN EN.CITE ADDIN EN.CITE.DATA], so the fetal HPT may not be able to adjust output in the face of reduced maternal fT4 supply and increased perchlorate transfer.

Perchlorate, like thiocyanate, selenium cyanate, and nitrate, competitively binds, in a dose-dependent manner, to the NIS and reduces iodide uptake by the thyroid gland. Recent work using a non-linear regression model shows that the Michaelis-Menten constant (K_m), which characterizes the binding affinity of perchlorate for the NIS, is approximately 0.59 μM, which is about 60% of that originally predicted [ADDIN EN.CITE <EndNote><Cite><Author>Schlosser</Author><Year>2016</Year><RecNum>293</RecNum><DisplayText>(Schlosser, 2016)</DisplayText><record><rec-number>293</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1470167034">293</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Schlosser, P. M.</author></authors></contributors><auth-address>US EPA, National Center for Environmental Assessment, Washington, DC, USA.</auth-address><titles><title>Revision of the affinity constant for perchlorate binding to the sodium-iodide symporter based on in vitro and human in vivo data</title><secondary-title>Journal of Applied Toxicology</secondary-title></titles><periodical><full-title>Journal of Applied Toxicology</full-

title></periodical><edition>2016/05/14</edition><dates><year>2016</year><pub-dates><date>May 13</date></pub-dates></dates><isbn>1099-1263 (Electronic)
0260-437X (Linking)</isbn><accession-num>27177048</accession-num><urls></urls><electronic-resource-num>10.1002/jat.3337</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>Eng</language></record></Cite></EndNote>]. This means that approximately half as much perchlorate is required to out-compete iodide than suggested by earlier models. Since both iodide and perchlorate would be consumed during the day, changes in dietary intake, uptake, and competition between the two ions will vary depending on the foods consumed and water sources, and the rate of clearance of each ion from circulation.

2.6 Physiologic Connection between Thyroid Hormone Levels and Neurodevelopment

The profound effects of thyroid deficiencies during development were first documented in children with congenital hypothyroidism by Paracelsus [ADDIN EN.CITE <EndNote><Cite><Author>Cranefield</Author><Year>1963</Year><RecNum>1892</RecNum><DisplayText>(Cranefield & Federn, 1963)</DisplayText><record><rec-number>1892</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497969366">1892</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Cranefield, P.</author><author>Federn, W.</author></authors></contributors><titles><title>Paracelsus on goiter and cretinism: A translation and discussion of "De Struma, Vulgo Der Kropf"</title><secondary-title>Bulletin of the History of Medicine</secondary-title></titles><periodical><full-title>Bulletin of the History of Medicine</full-title></periodical><pages>463-471</pages><volume>37</volume><dates><year>1963</year></dates><urls></urls></record></Cite></EndNote>]. Modern studies demonstrate that unless treated, children with congenital hypothyroidism will suffer from problems associated with somatic growth and an array of visuomotor and neurocognitive deficits. Aberrant patterns of growth, development, and organization of the cortex, cerebellum, hippocampus, basal ganglia, and brain stem can all result from reduced thyroid hormone exposure during development [ADDIN EN.CITE <EndNote><Cite><Author>Williams</Author><Year>2008</Year><RecNum>193</RecNum><DisplayText>(G. Williams, 2008; Zoeller & Rovet, 2004)</DisplayText><record><rec-number>193</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202836">193</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, GR</author></authors></contributors><titles><title>Neurodevelopmental and neurophysiological actions of thyroid hormone</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>784-794</pages><volume>20</volume><number>6</number><dates><year>2008</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet, J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental

findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>].

Thyroid hormones are essential for the development and differentiation of the developing brain. The brain and spinal cord begin development in the first half of the first trimester. fT4 passes through the blood-brain barrier via multiple, specific transporter proteins. Next, T4 is converted to T3 by the developing glial cells and then transported to neurons. T3 then interacts with nuclear receptors to tightly regulate gene expression so that neurogenesis, synaptogenesis, neuronal migration, cell differentiation, and myelination are developmentally appropriate. Deficiencies in thyroid hormones through iodine deficiency, congenital hypothyroidism, or maternal hypothyroidism/hypothyroxinemia can result in neurological impairments and intellectual deficits [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2000</Year><RecNum>1885</RecNum><DisplayText>(G Morreale de Escobar, Obregón, & Escobar del Rey, 2000)</DisplayText><record><rec-number>1885</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1496433675">1885</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F.</author></authors></contributors><titles><title>Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia?</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>3975-3987</pages><volume>85</volume><number>11</number><dates><year>2000</year></dates><urls></urls></record></Cite></EndNote>].

The fetal thyroid gland first begins to concentrate iodide at about 11–12 weeks and begins significant contribution to fetal development around 16 weeks. However, the developing fetus still relies on some supply of maternal thyroid hormones, primarily fT4, until birth [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(G Morreale de Escobar, Obregón, & Escobar del Rey, 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437077734">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>]. The fetal thyroid is not fully mature until birth, so premature birth can also be associated with low thyroid hormone concentrations. Thus, alterations in thyroid

hormone levels can impact brain development in a variety of ways depending on when the alteration occurs and for how long.

For example, early in brain development, fT4 deficiency can affect neuronal cell proliferation and cell migration in the hippocampus (essential for learning and memory, cognitive function), the cerebral cortex (essential for executive function, cognitive function), and the medial ganglionic eminence (transitory development structure responsible for guiding axonal migration) [ADDIN EN.CITE <EndNote><Cite><Author>Williams</Author><Year>2008</Year><RecNum>193</RecNum><DisplayText>(G. Williams, 2008)</DisplayText><record><rec-number>193</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202836">193</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, GR</author></authors></contributors><titles><title>Neurodevelopmental and neurophysiological actions of thyroid hormone</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>784-794</pages><volume>20</volume><number>6</number><dates><year>2008</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>]. Maternal hypothyroidism or hypothyroxinemia at these early stages may result in problems with gross motor skills and visual attention and processing [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><DisplayText>(Zoeller & Rovet, 2004)</DisplayText><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet, J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>]. As the first trimester progresses, increases in hCG result in a higher production of T4 [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2007</Year><RecNum>201</RecNum><DisplayText>(G Morreale de Escobar et al., 2007)</DisplayText><record><rec-number>201</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466438813">201</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, María Jesús</author><author>Escobar del Rey, F. </author></authors></contributors><titles><title>Iodine deficiency and brain development in the first half of pregnancy</title><secondary-title>Public Health Nutrition</secondary-title></titles><periodical><full-title>Public health nutrition</full-title></periodical><pages>1554-1570</pages><volume>10</volume><number>12A</number><dates><year>2007</year></dates><isbn>1475-2727</isbn><urls></urls></record></Cite></EndNote>]. In addition, serum TBG increases during the first trimester, remaining elevated throughout pregnancy because estrogen increases the glycosylation of TBG, increasing its serum half-life. In the fetus this period also corresponds to neurogenesis in the midbrain and cortex, neuronal migration into the cortex,

deiodinase activity for conversion of T4 to T3, and presence of nuclear thyroid receptors in the brain [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(G Morreale de Escobar et al., 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437077734">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>].

Higher levels of maternal fT4 throughout pregnancy allow for normal neuron and glial cell migration and differentiation, axonal growth, dendritic branching, neurogenesis, and synaptogenesis to occur [ADDIN EN.CITE <EndNote><Cite><Author>Williams</Author><Year>2008</Year><RecNum>193</RecNum><DisplayText>(G. Williams, 2008)</DisplayText><record><rec-number>193</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202836">193</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, GR</author></authors></contributors><titles><title>Neurodevelopmental and neurophysiological actions of thyroid hormone</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>784-794</pages><volume>20</volume><number>6</number><dates><year>2008</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>]. The complex interconnectedness of brain regions required for normal function could be impaired by effects on all of these processes simultaneously or in sequence, and across multiple brain regions. Maternal thyroid deficiencies during these processes further affect visual processing, development of fine motor skills, IQ, and selective learning problems [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><DisplayText>(Zoeller & Rovet, 2004; Zoeller et al., 2007)</DisplayText><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet, J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-

2826</isbn><urls></urls></record></Cite><Cite><Author>Zoeller</Author><Year>2007</Year><RecNum>186</RecNum><record><rec-number>186</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202457">186</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Tan, Shirlee W</author><author>Tyl, Rochelle W</author></authors></contributors><titles><title>General background on the hypothalamic-pituitary-thyroid (HPT) axis</title><secondary-title>Critical Reviews in Toxicology</secondary-title></titles><periodical><full-title>Critical reviews in toxicology</full-title></periodical><pages>11-53</pages><volume>37</volume><number>1-2</number><dates><year>2007</year></dates><isbn>1040-8444</isbn><urls></urls></record></Cite></EndNote>]. Additionally, concern is emerging that there may be adverse effects associated with fT4 levels above the normal range (Korevaar et al., 2016).

Additionally, humans continue to undergo considerable post-natal brain development well through puberty and into early adulthood. A properly functioning HPT is necessary for proper neurologic development at this stage [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2004</Year><RecNum>194</RecNum><DisplayText>(Zoeller & Rovet, 2004)</DisplayText><record><rec-number>194</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202917">194</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Rovet, J</author></authors></contributors><titles><title>Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings</title><secondary-title>Journal of Neuroendocrinology</secondary-title></titles><periodical><full-title>Journal of neuroendocrinology</full-title></periodical><pages>809-818</pages><volume>16</volume><number>10</number><dates><year>2004</year></dates><isbn>1365-2826</isbn><urls></urls></record></Cite></EndNote>]. This is particularly true in the hippocampus, which is considered to have a relatively high degree of neuroplasticity in humans and undergoes considerable adult neurogenesis. How the behavioral and cognitive deficits associated with subclinical hypothyroidism and hypothyroxinemia are manifested within the brain is a research area where further evaluation is needed.

3. Overview of the EPA's Biologically Based Dose-Response Model for Perchlorate's Impact on Thyroid Hormone Levels

The EPA intends to inform the derivation of the MCLG for perchlorate by utilizing a BBDR model for early pregnancy to predict the impact that perchlorate will have on serum thyroid hormone levels at a given iodine intake (Step 1 of [REF _Ref417634154 \h]). This section summarizes the history of the development of the BBDR model along with its current structure (Section [REF _Ref482890532 \r \h]). Further details are provided on key model parameters and attributes (Section [REF _Ref482890596 \r \h] and Section [REF _Ref484089893 \r \h]), which is followed by a summary of results relevant to this analysis (Section [REF _Ref483494050 \r \h]). Lastly, there is a discussion of potential uncertainties associated with the model (Section [REF _Ref482972894 \r \h]). The BBDR model overview provided here is supported by detailed descriptions in Appendix A.

The BBDR model can be described as containing two main components: (1) a pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism, and excretion of these two anions; and (2) a pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, most significantly T4. The pharmacokinetic portion contains a physiological description (organ volumes, blood flows) and chemical-specific information (partition coefficients, volume of distribution, rate constants for transport, metabolism, and elimination) that enable a prediction of perchlorate and iodide internal concentration at the critical target (i.e., thyroidal NIS) in association with a particular exposure scenario (route of exposure, age, dose level). This portion of the model is similar to other physiologically based pharmacokinetic models and for perchlorate is simplified by the absence of metabolism. The pharmacodynamic portion of the model uses this internal concentration to simulate how the chemical will act within a known mode of action to perturb host systems and lead to a toxic effect. Thus, BBDR modeling attempts to predict the internal dose of a chemical associated with a particular exposure scenario and the perturbation this internal dose can have on host systems.

3.1 Background and Structure of BBDR Model Development

In 2012, the EPA sought advice from the SAB on how best to consider and interpret life stage information, epidemiologic and biomonitoring data, PBPK analyses, and the totality of perchlorate health information to derive an MCLG for perchlorate. In 2013, the SAB recommended the following [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><DisplayText>(SAB, 2013)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>]:

- Derive a perchlorate MCLG that addresses sensitive life stages through PBPK/PD modeling;

- "Expand the modeling approach to account for thyroid hormone perturbations and potential adverse neurodevelopmental outcomes from perchlorate exposure;
- Utilize a mode-of-action framework for developing the MCLG that links the steps in the proposed mechanism leading from perchlorate exposure through iodide uptake inhibition to thyroid hormone changes and finally neurodevelopmental impacts; [and]
- Extend the [BBDR] model expeditiously to…provide a key tool for linking early events with subsequent events as reported in the scientific and clinical literature on iodide deficiency, changes in thyroid hormone levels, and their relationship to neurodevelopmental outcomes during sensitive early life stages" (SAB, 2013, p. 19).

The SAB stated that this data-driven approach represents a more rigorous way to address differences in biology and exposure between adults and sensitive life stages than is possible with the default approach for deriving an MCLG, and that the EPA should also consider available data on potential adverse health effects (neurodevelopmental outcomes) due to perturbations in thyroid hormone levels regardless of the cause of those perturbations (SAB, 2013).

Based on the SAB's recommendations, the EPA, with contributions from FDA, first developed and integrated PBPK models for perchlorate and iodide with BBDR models for thyroid hormones to predict the effect of perchlorate on the thyroid gland in formula-fed and breastfed infants for the post-natal period from days 7 to 90, as well as lactating women and third-trimester pregnant women and her fetus. This draft version of the developed model was intended to be valid for fT4 levels ranging from euthyroid to as low as hypothyroxinemia, in which fT4 levels are decreased to the lower end of the normal (i.e., within the population reference) range and TSH levels remain within the normal range [ADDIN EN.CITE
<EndNote><Cite><Author>Silva</Author><Year>1981</Year><RecNum>261</RecNum><DisplayText>(Silva & Silva, 1981)</DisplayText><record><rec-number>261</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468519119">261</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Silva, J. E.</author><author>Silva, S.</author></authors></contributors><titles><title>Interrelationships among serum thyroxine, triiodothyronine, reverse triiodothyronine, and thyroid-stimulating hormone in iodine-deficient pregnant women and their offspring: effects of iodine supplementation</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>671-7</pages><volume>52</volume><number>4</number><edition>1981/04/01</edition><keywords><keyword>Female</keyword><keyword>Fetal Blood/analysis</keyword><keyword>Humans</keyword><keyword>Infant, Newborn</keyword><keyword>Iodides/urine</keyword><keyword>Iodine/ deficiency/therapeutic use</keyword><keyword>Pregnancy</keyword><keyword>Pregnancy Complications/ blood</keyword><keyword>Thyrotropin/ blood</keyword><keyword>Thyroxine/ blood</keyword><keyword>Triiodothyronine/ blood</keyword><keyword>Triiodothyronine, Reverse/ blood</keyword></keywords><dates><year>1981</year><pub-dates><date>Apr</date></pub-dates></dates><isbn>0021-972X (Print)
0021-972X (Linking)</isbn><accession-num>7204539</accession-num><urls></urls><electronic-resource-

num>10.1210/jcem-52-4-671</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. The model was limited to the range of perchlorate doses and dietary iodine intakes for which thyroid hormone levels are assumed to be maintained within a reference range without action of the TSH feedback mechanism.[5]

The model was subjected to external peer review in January 2017. The final peer review report titled *External Peer Review for EPA's Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water* is available through the docket at [HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0439-0006"].

The EPA considered all of the peer reviewers' recommendations and focused on those that were anticipated to be most important for increasing the scientific rigor of the model and modeling results. These revisions are summarized in this section; additional detail is available in Appendix A. Model revisions focused on the following key recommendations:

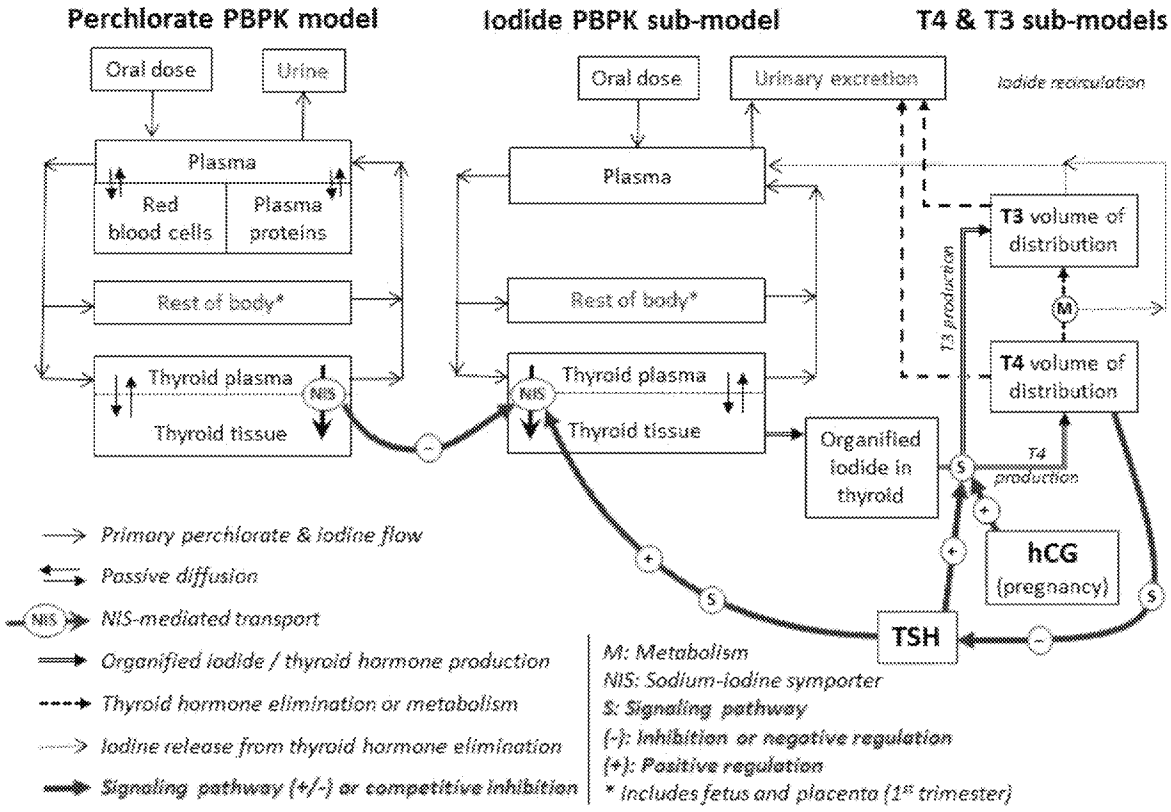
- Extending the model to early pregnancy;
- Incorporating biological feedback control of hormone production via TSH signaling, such that the model can describe lower levels of iodide nutrition;
- Calibrating the model and evaluating its behavior for upper and lower percentiles of the distribution of thyroid hormone levels in the population, as well as the population median thyroid hormone levels; and
- Conducting an uncertainty analysis for key parameters.

The BBDR model for which an overview is provided in this section and in [REF _Ref482868704 \h] is described in complete detail in Appendix A. In this model, the EPA simulated the uptake and disposition of iodide and perchlorate and their competitive interaction with the thyroidal NIS within the thyroid and elsewhere in the body. Based upon the availability of iodide, thyroid hormone synthesis, distribution, and metabolic transformation are modeled to yield predictions of blood levels of T4 and T3 (i.e., total T4, fT4, free T3 (fT3), and total T3 (tT3)). Further, a TSH feedback loop has been incorporated in which TSH levels are simulated based upon the predicted level of fT4 according to the relationship between those hormones as observed in humans. In particular, a decrease in fT4 is predicted to increase blood TSH, the response to which is an increase in the thyroidal NIS expression, resulting in higher NIS activity. Increased blood TSH is also assumed to increase the production rate constants for T4 and T3. The BBDR model was first developed for non-pregnant women and then extended to pregnancy by incorporating time-dependent parameters based on changes observed in early pregnancy through gestational week (GW) 16. The BBDR model is designed to assess long-

[5] For a more detailed discussion on the development of the draft model, its calibration, and dose-response evaluations, please see the draft BBDR model report titled *Biologically Based Dose Response Models for the Effect of Perchlorate on Thyroid Hormones in the Infant, Breast Feeding Mother, Pregnant Mother, and Fetus: Model Development, Revision, and Preliminary Dose-Response Analysis.* The report is available through the docket at [HYPERLINK "http://www.regulations.gov"] *(Docket ID No. EPA-HQ-OW-2016-0439-0006).*

term, steady-state conditions in the non-pregnant woman and week-to-week variation in pregnancy, rather than short-term (hour-to-hour or day-to-day) fluctuations. Appendix A includes sensitivity and uncertainty analyses of the updated model.

Figure [SEQ Figure * ARABIC]. Overview of the Structure of the Early Pregnancy BBDR Model



As described in Section [REF _Ref482958608 \r \h], the decision to focus on early pregnancy was based on the fact that the epidemiology supporting the relationship between maternal thyroid hormone levels and subsequent neurodevelopmental outcomes is stronger for deficits in fT4 during the first trimester as opposed to later in pregnancy (e.g., Pop et al., 1999, 2002). Given this focus on early pregnancy, the structure of the BBDR model is simplified from that of the previously described late-gestation model (previously reviewed in January 2017, based on Lumen et al., 2013), based upon the understanding that the fetal thyroid gland does not begin functioning until the second half of pregnancy. During early pregnancy, thyroid hormone-dependent neurodevelopment is driven by the supply of maternal thyroid hormone (in particular, serum concentrations of fT4) (Morreale de Escobar et al., 2004). Further, the epidemiology supporting this effect is stronger for first-trimester deficits in fT4 as opposed to later in pregnancy (Pop et al., 1999, 2002). In particular, the present model has been refined to focus on predicting maternal thyroid hormone levels during early pregnancy.

This model structure ([REF _Ref482868704 \h]) is adapted from the third-trimester model of Lumen et al. (2013)[6] and the lactation iodide/thyroid hormone model of Fisher et al. (2016) with simplifications of some aspects and elaboration and adjustments of others. The model is comprised of submodels for perchlorate, iodide, T4, and T3. The six compartments used for perchlorate and iodide in the third-trimester BBDR model of Lumen et al. (2013) were condensed to essentially three compartments: plasma, thyroid, and "rest of body" (ROB). This choice is justified because the fetus and its constituent compartments are much smaller in the first trimester, and therefore it was deemed unnecessary to explicitly consider them. For example, at the end of the first trimester the fetus is expected to weigh less than 0.15 kg. To be clear, the placenta and fetus mass are included in the maternal ROB, and condensation of other maternal compartments into one compartment is not expected to significantly affect the predicted concentrations of the key anions and hormones given that they are described for long-term, continuous ingestion of iodine and perchlorate. Partitioning of perchlorate into red blood cells and binding to plasma protein are included in this model, unlike that of Lumen et al. (2013). Passive diffusion of perchlorate between plasma and red blood cells was included in the original human perchlorate PBPK model of Merrill et al. (2005) based on observations that iodide likewise distributed into red blood cells [ADDIN EN.CITE <EndNote><Cite><Author>Rall</Author><Year>1950</Year><RecNum>2210</RecNum><DisplayText>(Rall, Power, & Albert, 1950)</DisplayText><record><rec-number>2210</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

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[6] During the development of this report, a study by Lumen & George [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lumen</Author><Year>2017</Year><RecNum>1912</RecNum><DisplayText>(2017a)</DisplayText><record><rec-number>1912</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503406753">1912</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lumen, A.</author><author>George, N.I.</author></authors></contributors><titles><title>Estimation of iodine nutrition and thyroid function status in late-gestation pregnant women in the United States: Development and application of a population-based pregnancy model</title><secondary-title>Toxicology and Applied Pharmacology</secondary-title></titles><periodical><full-title>Toxicology and applied pharmacology</full-title></periodical><pages>24-38</pages><volume>314</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>] was published that extended the Lumen et al. (2013) model to include more severe iodine deficiency conditions, incorporate the effects of homeostatic mechanisms, and develop the extended model into a population-based model. Another study by Lumen & George [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lumen</Author><Year>2017</Year><RecNum>1913</RecNum><DisplayText>(2017b)</DisplayText><record><rec-number>1913</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503406958">1913</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lumen, A.</author><author>George, N.I.</author></authors></contributors><titles><title>Evaluation of the risk of perchlorate exposure in a population of late-gestation pregnant women in the United States: Application of probabilistic biologically-based dose response modeling</title><secondary-title>Toxicology and Applied Pharmacology</secondary-title></titles><periodical><full-title>Toxicology and applied pharmacology</full-title></periodical><pages>9-14</pages><volume>322</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>] integrated the calibrated perchlorate exposure model from Lumen et al. (2013) into the population-based model in Lumen and George (2017a). Lumen and George (2017b) used Monte Carlo sampling and probabilistic simulation to quantify the distribution of urinary perchlorate for late-gestation pregnant women and to conduct an uncertainty analysis of influential perchlorate-specific parameters.

timestamp="1542316851">2210</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rall, J.E.</author><author>Power, M.H.</author><author>Albert, A.</author></authors></contributors><titles><title>Distribution of radioiodine in erythrocytes and plasma of man</title><secondary-title>Proceedings of the Society for Experimental Biology and Medicin</secondary-title></titles><periodical><full-title>Proceedings of the Society for Experimental Biology and Medicin</full-title></periodical><pages>460-461</pages><volume>74</volume><number>2</number><dates><year>1950</year></dates><urls></urls></record></Cite></EndNote>]. Hays and Green [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Hays</Author><Year>1973</Year><RecNum>2209</RecNum><DisplayText>(1973)</DisplayText><record><rec-number>2209</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1542316779">2209</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hays, M.T.</author><author>Green, F.A.</author></authors></contributors><titles><title>In vitro studies of 99mTc-pertechnetate binding by human serum and tissues</title><secondary-title>Journal of Nuclear Medicine</secondary-title></titles><periodical><full-title>Journal of Nuclear Medicine</full-title><abbr-1>J Nucl Med</abbr-1></periodical><pages>149-158</pages><volume>14</volume><number>3</number><dates><year>1973</year></dates><urls></urls></record></Cite></EndNote>] and Scatchard and Black [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Scatchard</Author><Year>1949</Year><RecNum>2211</RecNum><DisplayText>(1949)</DisplayText><record><rec-number>2211</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1542316918">2211</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Scatchard, G.</author><author>Black, E.S.</author></authors></contributors><titles><title>The effect of salts on the isoionic and isoelectric points of proteins</title><secondary-title>The Journal of Physical Chemistry</secondary-title></titles><periodical><full-title>The Journal of Physical Chemistry</full-title></periodical><pages>88-99</pages><volume>53</volume><dates><year>1949</year></dates><urls></urls></record></Cite></EndNote>] demonstrated binding of perchlorate to human plasma proteins.

The BBDR model is dependent on the known physiological mechanisms that occur in the thyroid as they relate to iodide and perchlorate exposure as summarized in Section [REF _Ref482959130 \r \h] [ADDIN EN.CITE <EndNote><Cite><Author>Zoeller</Author><Year>2007</Year><RecNum>186</RecNum><Prefix>for review see </Prefix><DisplayText>(for review see Zoeller et al., 2007)</DisplayText><record><rec-number>186</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1466202457">186</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zoeller, R Thomas</author><author>Tan, Shirlee W</author><author>Tyl, Rochelle W</author></authors></contributors><titles><title>General background on the hypothalamic-pituitary-thyroid (HPT) axis</title><secondary-title>Critical Reviews in Toxicology</secondary-title></titles><periodical><full-title>Critical reviews in toxicology</full-title></periodical><pages>11-53</pages><volume>37</volume><number>1-2</number><dates><year>2007</year></dates><isbn>1040-8444</isbn><urls></urls></record></Cite></EndNote>]. That is, within the iodide submodel, iodide

is consumed and enters the plasma. From the plasma, iodide can be transported to the thyroid. In the thyroid, T3 and T4 are formed when Tg produced by the thyroid follicular cells is combined with iodide; this combined Tg-iodide is identified as "organified" or "bound" iodide in the model. Release of T4 and T3 into circulation is assumed to draw from this common thyroidal pool.

Because the model time-scale for changes in hormone levels is in weeks, while variation in TSH is known to occur on a much faster time-scale, it was deemed unnecessary to explicitly describe the production, distribution, and clearance of TSH. Instead, TSH is assumed to respond immediately to any changes in fT4, with TSH being a decreasing function of fT4: the higher the serum fT4 concentration, the lower TSH. The activity (Vmax) for NIS-mediated uptake of iodide (and perchlorate) by the thyroid and rate constants for production of T4 and T3 are then assumed to increase as TSH increases, leading to a negative feedback loop. However, the response of fT4 to this feedback is not instantaneous, since it takes time for an increased production rate to lead to increased circulating levels of fT4.

While any decrease in fT4 leads to an increase in TSH, the relationship is nonlinear with less of a change in TSH per unit change in fT4 when fT4 is in the euthyroid range than outside of it, based on observational data (Hadlow et al., 2013). Likewise, increases in fT4 lead to decreases in TSH.

In addition to regulation by TSH, hCG levels rise in early pregnancy. and this increases T4 production. (The Vmax for NIS-mediated uptake is also increased during pregnancy based on independent data [ADDIN EN.CITE <EndNote><Cite><Author>Aboul-Khair</Author><Year>1964</Year><RecNum>361</RecNum><Suffix>`; see Appendix A`, 1.4.11</Suffix><DisplayText>(Aboul-Khair, Crooks, Turnbull, & Hytten, 1964; see Appendix A, 1.4.11)</DisplayText><record><rec-number>361</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206424">361</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Aboul-Khair, S. A.</author><author>Crooks, J.</author><author>Turnbull, A. C.</author><author>Hytten, F. E.</author></authors></contributors><titles><title>The physiological changes in thyroid function during pregnancy</title><secondary-title>Clinical Science</secondary-title><alt-title>Clin Sci (Lond)</alt-title><short-title>Clinical Science</short-title></titles><periodical><full-title>Clinical Science</full-title><abbr-1>Clin Sci (Lond)</abbr-1></periodical><alt-periodical><full-title>Clinical Science</full-title><abbr-1>Clin Sci (Lond)</abbr-1></alt-periodical><pages>195-207</pages><volume>27</volume><dates><year>1964</year></dates><isbn>ISSN 0143-5221
EISSN 1470-8736</isbn><label>2140787</label><urls></urls><language>English</language></record></Cite></EndNote>], but that change is not described as an explicit function of hCG.) The stimulatory and feedback pathways are indicated by the thick, solid, red arrows (identified as "signaling pathways") in [REF _Ref482868704 \h]. The perchlorate submodel is analogous to that of the iodide model and describes the assumed mode of action for perchlorate. That is, once perchlorate is consumed it is distributed throughout the body, including to the thyroid plasma, it binds to an anion binding site on NIS, where it competitively inhibits the binding and translocation of iodide to the cytosol. This inhibition reduces the thyroid's stores of organified iodide, and hence decreases the rate of formation and release of T3 and T4. As fT4 levels decline, the predicted concentration of TSH increases, thereby stimulating iodide uptake and thyroid hormone production, allowing for a partial compensation for the inhibition: the resulting decline in fT4 is less than it would be in the absence of this mechanism.

Subsequent sections describe key parameters in the model. Details regarding model calibration and the underlying mathematical functions of the submodels are provided in Appendix A.

3.2 Summary of Key BBDR Model Parameters

The current BBDR model is built upon previous models of the thyroid for pregnancy [ADDIN EN.CITE <EndNote><Cite><Author>Merrill</Author><Year>2005</Year><RecNum>339</RecNum><DisplayText>(Merrill, 2005)</DisplayText><record><rec-number>339</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1494877307">339</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Merrill, EA; Clewell, RA; Robinson, PJ; Jarabek, AM; Gearhart, JM; Sterner, TR; Fisher, JW</author></authors></contributors><titles><title>PBPK model for radioactive iodide and perchlorate kinetics and perchlorate-induced inhibition of iodide uptake in humans</title><secondary-title>Toxicological Sciences</secondary-title></titles><periodical><full-title>Toxicological Sciences</full-title></periodical><pages>25-43</pages><volume>83</volume><dates><year>2005</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">http://dx.doi.org/10.1093/toxsci/kfi017</style></url></related-urls></urls></record></Cite></EndNote>] [ADDIN EN.CITE <EndNote><Cite><Author>Lumen</Author><Year>2013</Year><RecNum>107</RecNum><DisplayText>(Lumen et al., 2013)</DisplayText><record><rec-number>107</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1450367396">107</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lumen, A.</author><author>Mattie, D.R.</author><author>Fisher, J.W.</author></authors></contributors><titles><title>Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model</title><secondary-title>Toxicological Sciences</secondary-title></titles><periodical><full-title>Toxicological Sciences</full-title></periodical><pages>320-341</pages><volume>133</volume><number>2</number><section>320</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1093/toxsci/kft078</electronic-resource-num></record></Cite></EndNote>] and lactation [ADDIN EN.CITE <EndNote><Cite><Author>Fisher</Author><Year>2016</Year><RecNum>250</RecNum><DisplayText>(Fisher, Wang, George, Gearhart, & McLanahan, 2016)</DisplayText><record><rec-number>250</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468416471">250</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fisher, J</author><author>Wang, Jian</author><author>George, Nysia I.</author><author>Gearhart, Jeffery M.</author><author>McLanahan, Eva D.</author></authors></contributors><titles><title>Dietary iodine sufficiency and moderate insufficiency in the lactating mother and nursing infant: A computational perspective</title><secondary-title>PLoS ONE</secondary-title></titles><periodical><full-title>PLoS ONE</full-title></periodical><pages>e0149300</pages><volume>11</volume><number>3</number><dates><year>2016</year></dates><publisher>Public Library of Science</publisher><urls><related-urls><url><style face="underline" font="default"

size="100%">http://dx.doi.org/10.1371%2Fjournal.pone.0149300</style></url></related-urls></urls><electronic-resource-num>10.1371/journal.pone.0149300</electronic-resource-num></record></Cite></EndNote>] with two major alterations for the current purpose: (1) adaptation for the non-pregnant woman and early pregnancy up to 16 GW; and (2) incorporation of the TSH feedback loop. The EPA made various additional modifications in the process of examining the model code and fits to underlying data. [REF _Ref483397647 \h] and the subsequent text provide an overview of key model parameters and describe both how these parameters were derived and how they may differ from previous versions of the model. This table does not summarize all the BBDR model parameters. A more complete accounting of all model parameters is provided in Appendix A.

Table [SEQ Table * ARABIC]. Summary of Major Features of Current BBDR Modeling

Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
Iodide Submodel	
Partition coefficient (PC) ROB: blood = (Prob_I) 0.243	The current model uses a weighted average of tissue-specific PCs for the new ROB compartment that is adjusted for NIS-mediated uptake in skin [ADDIN EN.CITE <EndNote><Cite><Author>Slominski</Author><Year>2002</Year><RecNum>2212</RecNum><DisplayText>(Slominski et al., 2002)</DisplayText><record><rec-number>2212</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1542317105">2212</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Slominski, A.</author><author>Wortsman, J.</author><author>Kohn, L.</author><author>Ain, K.B.</author><author>Venkataraman, G.M.</author><author>Pisarchik, A.</author><author>Chung, J.H.</author><author>Giuliani, C.</author><author>Thornton, M.</author><author>Slugocki, G.</author><author>Tobin, D.J.</author></authors></contributors><titles><title>Expression of hypothalamic–pituitary–thyroid axis related genes in the human skin</title><secondary-title>Journal of Investigative Dermatology</secondary-title></titles><periodical><full-title>Journal of Investigative Dermatology</full-title><abbr-1>J Invest Dermatol</abbr-1></periodical><pages>1449-1455</pages><volume>119</volume><number>6</number><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] and mammary glands. The adjustment for the skin and mammary NIS increased the PC by 20%. Lumen et al. (2013) reported PCs for iodide for individual tissues that ranged from 0.15 to 0.4, which were used as-is in the January 2017 model.
Plasma protein binding of iodide = N/A	Not modeled in current BBDR model or January 2017.
Uptake into thyroid via NIS Thyroid Iodide Uptake (VmaxNISF_t	The current model uses the same saturable Michaelis-Menten approach specifying a scaled Vmax (VmaxNISF_thy_I) and K_m (KmNIS_I) for iodide, which is inhibited by perchlorate. Further, it uses the same K_m as used in the Lumen et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lumen</Author><Year>2013</Year><RecNum>107</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>107</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1450367396">107</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lumen,

Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
hy_I) = 690 nmol/h/kg$^{0.75}$ (non-pregnant value; this is scaled for pregnancy); NIS affinity (KmNIS_I) = 31.5 µM	A.</author><author>Mattie, D.R.</author><author>Fisher, J.W.</author></authors></contributors><titles><title>Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model</title><secondary-title>Toxicological Sciences</secondary-title></titles><periodical><full-title>Toxicological Sciences</full-title></periodical><pages>320-341</pages><volume>133</volume><number>2</number><section>320</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1093/toxsci/kft078</electronic-resource-num></record></Cite></EndNote>] model. The current model uses a 5.6-fold lower VmaxC compared to that in Lumen et al. (2013). This is based on fitting the data of female subjects from Greer et al. (2002). Further, VmaxC is scaled to increase with pregnancy based on an empirical relationship between gestational age and radioactive iodide uptake (see Appendix A).
Iodide from T4 and T3 deiodination based upon degradation rate of T4 (KdegT4F) and T3 (KdegT3F) KdegT4F = 1.9 x 10^{-5} L/hr/kg$^{0.75}$ KdegT3F = 1.7 x 10^{-4} L/hr/kg$^{0.75}$	The current model decreases KdegT4F and KdegT3F by a factor of 10 compared to the Lumen et al. (2013) values of 1.9 x 10^{-4} and 1.7x10^{-3} L/hr/kg$^{0.75}$, respectively. The decrease enables fitting of the model to the range of NHANES data, given uncertainties in other model parameters, with the procedure used by the EPA (see Appendix A, Section 2.2.3, for details). The current model uses the assumption from Lumen et al. (2013) that 50% of T4 degradation is due to T3 releasing one iodide ion, while the other 50% is completely degraded, yielding four iodide ions. The formula is: RdeiodT4=0.5(RdegT4 + 4*RdegT4) = 2.5*RdegT4 nmol/hr
Elimination to urine (CLFUI) = 0.0653 L/hr/kg$^{0.75}$ (non-pregnant value; this is scaled for pregnancy)	The current model begins with non-pregnant clearance of CLFUI = 0.0653 L/hr/kg$^{0.75}$ and increases over pregnancy by an empirical relationship between gestational age and iodide clearance (see Appendix A). Lumen et al. (2013) assumed that iodine clearance was a function of iodine intake, with the relationship fitted to data from Dunn & Delange [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Dunn</Author><Year>2005</Year><RecNum>711</RecNum><DisplayText>(2005)</DisplayText><record><rec-number>711</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206430">711</key></foreign-keys><ref-type name="Edited Book">28</ref-type><contributors><authors><author>Dunn, J. T.</author><author>Delange, F. M.</author></authors><secondary-authors><author>Braverman, L. E.</author><author>Utiger, R. D.</author></secondary-authors></contributors><titles><title>Iodine deficiency</title><secondary-title>Werner & Ingbar's the thyroid : a fundamental and clinical text</secondary-title></titles><pages>264-288</pages><dates><year>2005</year></dates><pub-location>Philadelphia, PA</pub-location><publisher>LippincottWilliams & Wilkins</publisher><label>2990711</label><urls></urls></record></Cite></EndNote>] for the subjects from multiple studies (not necessarily during pregnancy).

Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
Perchlorate Submodel	
PC ROB:serum = (Prob_P) 0.558	The current model uses a weighted average of tissue-specific PCs for the new ROB compartment and includes NIS uptake in skin and mammary glands. The inclusion of the skin and mammary NIS increased the PC by 80%. Lumen et al. (2013) reported PCs for perchlorate for individual tissues that ranged from 0.13 to 0.56.
Plasma protein binding (Km_Bp) = 0.181 μM	Included in the current model; not included in Lumen et al. (2013).
Distribution into red blood cells (RBCs), RBC:serum PRBC_P = 0.8	Included in the current model; not included in Lumen et al. (2013).
Uptake into thyroid via NIS (VmaxNISF_thy_P) = 650 nmol/h/kg$^{0.75}$ (non-pregnant value; this is scaled for pregnancy); (KmNIS_P) = 0.489 μM	The current model uses a K_m for perchlorate binding to the NIS (KmNIS_P) that is 3-fold lower than Lumen et al. (2013) (i.e., a 3-fold higher affinity). Specifically, K_m is the 2.5th percentile lower confidence limit of the population median based upon EPA reanalysis of Greer et al. (2002). The value (50th percentile = 0.73 μM) is similar to that obtained from re-analysis of *in vitro* binding data, 0.59 μM [ADDIN EN.CITE <EndNote><Cite><Author>Schlosser</Author><Year>2016</Year><RecNum>293</RecNum><DisplayText>(Schlosser, 2016)</DisplayText><record><rec-number>293</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1470167034">293</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Schlosser, P. M.</author></authors></contributors><auth-address>US EPA, National Center for Environmental Assessment, Washington, DC, USA.</auth-address><titles><title>Revision of the affinity constant for perchlorate binding to the sodium-iodide symporter based on in vitro and human in vivo data</title><secondary-title>Journal of Applied Toxicology</secondary-title></titles><periodical><full-title>Journal of Applied Toxicology</full-title></periodical><edition>2016/05/14</edition><dates><year>2016</year><pub-dates><date>May 13</date></pub-dates></dates><isbn>1099-1263 (Electronic)
0260-437X (Linking)</isbn><accession-num>27177048</accession-num><urls></urls><electronic-resource-num>10.1002/jat.3337</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>Eng</language></record></Cite></EndNote>]; use of KmNIS_P = 0.489 μM makes perchlorate 3 times more effective at competitive inhibition of NIS versus Lumen et al. (2013).

Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
Elimination to urine (CLFUP) = 0.105 L/hr/kg$^{0.75}$ (non-pregnant value; this is scaled for pregnancy)	The current model uses a higher urinary clearance compared to the clearance used in the Lumen et al. (2013) model (i.e., 0.05 L/hr/kg$^{0.75}$). The current model's clearance rate, CLFUP = 0.105 L/hr/kg$^{0.75}$, is for non-pregnant women and based on EPA reanalysis of Greer et al. (2002); it is the 2.5th percentile of the sampling distribution for the population median (see Appendix A), with the 50th percentile being 0.122 L/hr/kg$^{0.75}$. Urinary clearance increases over pregnancy by an empirical relationship between gestational age and glomerular filtration (see Appendix A). Lumen et al. (2013) fit a perchlorate clearance to Chilean [ADDIN EN.CITE <EndNote><Cite><Author>Téllez Téllez</Author><Year>2005</Year><RecNum>1707</RecNum><DisplayText>(Téllez Téllez et al., 2005)</DisplayText><record><rec-number>1707</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206446">1707</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Téllez Téllez, R.</author><author>Michaud Chacón, P.</author><author>Reyes Abarca, C.</author><author>Blount, B. C.</author><author>Van Landingham, C. B.</author><author>Crump, K. S.</author><author>Gibbs, J. P.</author></authors></contributors><titles><title>Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period</title><secondary-title>Thyroid</secondary-title><alt-title>Thyroid</alt-title><short-title>Thyroid</short-title></titles><periodical><full-title>Thyroid</full-title></periodical><alt-periodical><full-title>Thyroid</full-title></alt-periodical><pages>963-975</pages><volume>15</volume><number>9</number><dates><year>2005</year></dates><isbn>ISSN 1050-7256
EISSN 1557-9077</isbn><label>757207</label><urls><related-urls><url>http://dx.doi.org/10.1089/thy.2005.15.963</url></related-urls></urls><electronic-resource-num>10.1089/thy.2005.15.963</electronic-resource-num><language>English</language></record></Cite></EndNote>] pregnant women based upon estimated water intake. There were no data for dietary exposure in Téllez Téllez et al. (2005), so Lumen et al. (2013) effectively assumed zero dietary contribution to total exposure in their analysis.
T4 Synthesis	
Production of T4 (KProdT4F) = 5.83*10^{-7} L/hr/kg$^{.75}$ (non-pregnant value; this is scaled for pregnancy)	The current model uses a baseline first-order constant calibrated to NHANES 2007-2012 median, 10th, or 90th percentile non-pregnant data; the KProdT4F value for the median NHANES calibration is 5.83*10^{-7} L/hr/kg$^{0.75}$, which is lower than 2.45 x 10^{-6} used by Lumen et al. (2013) based on fitting to data of Nicoloff, Low, Dussault, & Fisher [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Nicoloff</Author><Year>1972</Year><RecNum>1321</RecNum><DisplayText>(1972)</DisplayText><record><rec-number>1321</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1321</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nicoloff, J. T.</author><author>Low, J. C.</author><author>Dussault, J. H.</author><author>Fisher, D. A.</author></authors></contributors><titles><title>Simultaneous measurement of thyroxine and triiodothyronine peripheral turnover kinetics in man</title><secondary-title>Journal of Clinical Investigation</secondary-title><alt-title>J Clin Invest</alt-title><short-title>Journal of Clinical Investigation</short-title></titles><periodical><full-title>Journal of Clinical Investigation</full-title></periodical><alt-periodical><full-title>J Clin Invest</full-title></alt-periodical><pages>473-483</pages><volume>51</volume><number>3</number><dates><year>1972</year></dates><isbn>ISSN 0021-9738
EISSN 1558-8238</isbn><label>2138452</label><urls><related-urls><url>http://dx.doi.org/10.1172/JCI106835</url></related-urls></urls><electronic-resource-num>10.1172/jci106835</electronic-resource-

Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
	num><language>English</language></record></Cite></EndNote>]. This value is scaled in pregnancy with increasing KProdT4 through GW 16 (peak occurring ~ GW 9) based upon placental hCG increase over this time according to the linear relationship from Glinoer [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Glinoer</Author><Year>1997</Year><RecNum>829</RecNum><DisplayText>(1997)</DisplayText><record><rec-number>829</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206432">829</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Glinoer, D.</author></authors></contributors><titles><title>The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology</title><secondary-title>Endocrine Reviews</secondary-title><alt-title>Endocr Rev</alt-title></titles><periodical><full-title>Endocrine Reviews</full-title></periodical><alt-periodical><full-title>Endocr Rev</full-title></alt-periodical><pages>404-433</pages><volume>18</volume><dates><year>1997</year></dates><isbn>ISSN 0163-769X
EISSN 0163769X</isbn><label>16513</label><urls></urls></record></Cite></EndNote>]: hCG_{reg} = 1 + 0.00354 x hCG.
TSH Feedback Loop	The current model incorporates a TSH feedback loop that adjusts the Vmax for uptake into the thyroid and production rate constants for T4 (KProdT4F) and T3 as TSH falls below or rises above its calibration point (i.e., the population percentile of TSH assumed to be consistent with the population percentiles of other thyroid hormones used for a particular calibration), in inverse relationship to corresponding increases or decreases in fT4. For example, when the model is calibrated to match median T4, T3, fT4, and fT3 levels, the median TSH level is selected as the calibration point, and regulation occurs as TSH goes above or below this level, in response to variation in fT4. The relationship between TSH and fT4 is explained by data in Hadlow et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Hadlow</Author><Year>2013</Year><RecNum>893</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>893</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206433">893</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hadlow, N. C.</author><author>Rothacker, K. M.</author><author>Wardrop, R.</author><author>Brown, S. J.</author><author>Lim, E. M.</author><author>Walsh, J. P.</author></authors></contributors><titles><title>The relationship between TSH and free T_4 in a large population is complex and nonlinear and differs by age and sex</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title><alt-title>J Clin Endocrinol Metab</alt-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><alt-periodical><full-title>J Clin Endocrinol Metab</full-title></alt-periodical><pages>2936-2943</pages><volume>98</volume><number>7</number><dates><year>2013</year></dates><isbn>ISSN 0021-972X
EISSN 1945-7197</isbn><label>3645386</label><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2012-4223</url></related-urls></urls><electronic-resource-num>10.1210/jc.2012-4223</electronic-resource-num><language>English</language></record></Cite></EndNote>] and further described below and in Appendix A. Lumen et al. (2013) did not have a TSH feedback loop.

Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
T4 Distribution	
T4 Volume of Distribution (VDFT40) = 0.162 L/kg (non-pregnant value; this is scaled for pregnancy)	The current model has a baseline value (0.162 L/kg) for non-pregnant women that is scaled to decrease linearly with gestation time through GW 16 based upon a study that measured the distribution of radio-labeled T4 in pregnant and non-pregnant women. See Appendix A for additional details. The absolute volume of distribution is VDT4 = VDFT40*BW, so the decrease in the relative volume is somewhat offset by increasing BW. Lumen et al. (2013) used an estimate of 0.11 L/kg for the third trimester.
Free (fT4) to tT4 Ratio (FRT40) = 1.03×10^{-4} (non-pregnant value; this is scaled for pregnancy)	The current model uses a baseline value of 1.03×10^{-4} for median non-pregnant women and then estimates the ratio during pregnancy based on an empirical relationship derived from the ratio by gestational week. This relationship is based upon six studies as shown in Appendix A. Lumen et al. (2013) estimated that the fraction of total T4 converted to fT4 was approximately 9.0×10^{-5}.
T4 Degradation	
KdegT4F = $1.9*10^{-5}$ L/hr/kg$^{0.75}$	T4 degradation in the current model was selected to allow model calibration to the range of thyroid hormone values in NHANES as described above in the iodide submodel section.
Additional Adjustments for Early Pregnancy	
Removal of placental and fetal compartments and condensing of maternal system to three compartments: serum, thyroid, and ROB	Simplification of BBDR model structure from Lumen et al. (2013); see [REF _Ref482868704 \h] and related adjustments to PCs, compartment volume, and flows.
fT4: total T4 median serum concentration ratio,	A polynomial regression for fT4 fit to five datasets describing initial increase and then decrease of fT4 during early pregnancy was divided by a Hill equation regression fit to five datasets describing the increase in total T4 during the first trimester. The resulting time-dependent fT4:T4 ratio (change vs. non-pregnant), which occurs due to increases in serum binding proteins, results in a decrease of approximately 30% in the fT4:T4 ratio during early pregnancy.

Key Elements and Parameter Values for Current Model	Sources, Derivation, and Differences from January 2017 (3rd trimester) Model (based on Lumen et al. (2013))
modeled to vary during early pregnancy	
Note: This table does not summarize all the BBDR model parameters. A more complete accounting of all model parameters is provided in Appendix A.	

3.3 Overview of Key Model Attributes That May Impact Thyroid Hormone Production

As described in [REF _Ref483397647 \h], the baseline non-pregnancy rate for T4 synthesis was developed by fitting NHANES 2007-2012 median, 10th, and 90th percentile data for non-pregnant women, with adjustment for increasing T4 production and varying fT4:T4 ratios during early pregnancy as seen in a number of studies (see Appendix A and related references (e.g., La'ulu & Roberts, 2011; Medici et al., 2012; Soldin et al., 2004; Stricker et al., 2007; Yan et al., 2011; Zhang et al., 2016)). There are several regulatory controls in the BBDR model that can impact T4 and T3 production, such as the inclusion of hCG in the model, varying iodine intake, and also the TSH feedback loop. The impact of hCG on T4 production is discussed in [REF _Ref483397647 \h]. Further details regarding how low iodine intake and the TSH feedback loop were considered in calibrating the model are presented below.

3.3.1 Low Iodine Intake

Plots of NHANES 2007-2012 data for non-pregnant women demonstrated little relationship between iodine intake and fT4, except possibly for iodine intake levels below 75 µg/day. Given limited data in this range, the EPA has used the relationship between thyroidal iodide stores (mg) and iodine intake, which shows depletion of fT4 at iodine intake levels below 100 µg/day [ADDIN EN.CITE <EndNote><Cite><Author>Delange</Author><Year>2000</Year><RecNum>682</RecNum><DisplayText>(Delange, 2000)</DisplayText><record><rec-number>682</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206429">682</key></foreign-keys><ref-type name="Edited Book">28</ref-type><contributors><authors><author>Delange, F. M.</author></authors><secondary-authors><author>Braverman, L. E.</author><author>Utiger, R. D.</author></secondary-authors></contributors><titles><title>Iodine deficiency</title></titles><pages>295-316</pages><edition>8th</edition><dates><year>2000</year></dates><pub-location>Philadelphia, PA</pub-location><publisher>Lippincott, Williams, and Wilkins</publisher><label>1247276</label><urls></urls><language>English</language></record></Cite></EndNote>]. This relationship was used as part of a parameter calibration procedure to simulate population percentiles of fT4, T4, T3, and TSH identified from NHANES data (see Appendix A, Figures 54-56).

3.3.2 TSH Feedback Loop

TSH increase in response to decreases in T4 has been captured in numerous studies that document the inverse relationship between these hormones. A compilation of data describing this relationship (Hadlow et al., 2013) has been analyzed by the EPA in Appendix A to enable TSH feedback loop incorporation into the BBDR model. The following equation elevates TSH in response to a lowered concentration of fT4, as might arise from goitrogen exposure or lowered iodine intake:

$$TSH(CfT4) = \frac{TSHtar \times TSHhad(CfT4)}{TSHhad(CfT4tar)}$$

In this equation, TSHtar is the "target" level of TSH in a population (percentile) or an individual corresponding to a given fT4 concentration (e.g., the median) in that population percentile or individual, and TSHhad(CfT4) is the empirical function fit to the collected fT4 and TSH data by Hadlow et al. (2013). For example, the median TSH concentration from NHANES data is associated with the median fT4 for the same population; so these two would be CfT4tar and TSHtar for the presumed median individual. Using that pair of values in the TSH equation above scales TSHhad(CfT4) such that when CfT4 = CfT4tar, TSH(CfT4) = TSHtar. This combination of target hormone levels is the set point where both are stable and TSH will not increase or decrease thyroid activity beyond the corresponding fT4 value. When fT4 concentration decreases TSH(CfT4) increases. The ratio, TSH(CfT4)/TSHtar, determines the degree to which the BBDR model will upregulate iodide uptake and T4 production (i.e., if TSHhad(CfT4) > TSHhad(CfT4tar)). The result is that the change in fT4 from the set point (CfT4tar) will be less than would occur in the absence of TSH feedback, but there will still be some change, hence a dose-response due to perchlorate.

The BBDR model achieves this feedback regulation by tuning three parameters, NIS Vmax (VmaxNISF_thy_I; i.e., modulation of number of symporter sites), KProdT4 (modulation of T4 synthesis rate), and KProdT3 (modulation of T3 synthesis rate). These three parameters are assumed to vary as $(TSH(CfT4)/TSHtar)^{pTSH}$, where the coefficient pTSH determines the strength of TSH stimulation. However, to estimate the value of pTSH one would need measurements of TSH and the thyroid-specific parameters that TSH is presumed to regulate—the Vmax for iodine uptake and the T4 and T3 production rate constants (the relationship between T4 and T3 production and thyroid iodide stores). Such data are not available for humans, so a nominal value of pTSH = 1 was tested. Using this value, model predictions appear to be consistent with median NHANES data for non-pregnant women (see Section 3.2 in Appendix A). Model runs with pTSH = 1 were used in evaluating the shift in the hypothyroxinemic population (Section [REF _Ref517191523 \r \h]). A lower bound of pTSH = 0.398, which is the ratio of a median value for TSH from NHANES (non-pregnant women) to the 97.5th percentile value from NHANES (non-pregnant women; details in Appendix A) was used for the dose-response analysis linking changes in fT4 to neurodevelopmental outcomes. This is based on an assumption that sensitive individuals with high TSH and average fT4 exist because the stimulus strength of TSH is proportionally weaker. TSH increases can drive corresponding increases in iodide uptake and T4 and T3 production as long as the iodide supply is sufficient. With decreasing iodine intake, colloidal iodide stores are modeled to decline, which ultimately impairs the thyroid's response to elevations in TSH. Using pTSH = 0.398 for the neurodevelopmental analysis ensures that the EPA is protecting a potentially sensitive population from adverse neurodevelopmental impacts. Using pTSH = 1 is more appropriate for an analysis of the shift in the hypothyroxinemic population given that the analysis is based on the full distribution of

fT4 levels and the approach aims to avoid the precursor effect to neurodevelopment (i.e., hypothyroxinemia).

3.4 Results of the BBDR Model

The BBDR model can predict serum thyroid hormone levels at specific gestational weeks, given levels of iodine intake and doses of perchlorate. [REF _Ref482950735 \h] displays plots that illustrate specific outputs of the model. The upper- and lower-bound simulations in this figure were developed using corresponding parameter sets for the median, upper, and lower bounds of fT4, T4, fT3, T3, and TSH. They are not true bounds, but are instead estimates for fT4 or TSH given NHANES data with median, 2.5th, and 97.5th percentiles for fT4, TSH, etc.

[REF _Ref482951228 \h] and [REF _Ref483557363 \h] summarize output of the BBDR model for various doses of perchlorate and gestational weeks and resulting fT4 and TSH levels at the median iodine intake (170 µg/day) and a low iodine intake, respectively. In both cases the model is calibrated to match median thyroid hormone levels given an ingestion of 90 µg/day of iodine—the median population as described in Appendix A. However, for [REF _Ref482951228 \h] and [REF _Ref483557363 \h], a weak level of TSH signaling strength, pTSH = 0.398, was used to illustrate the more sensitive dose-response from using that estimated lower bound. [REF _Ref512496933 \h] and [REF _Ref512496934 \h] report BBDR results using a median level of TSH signaling strength, or pTSH = 1. For analysis of a low-iodine population an iodine intake level of 75 µg/day was selected. This intake level represents between the 15th and 20th percentile of the population distribution of estimated iodine intake from NHANES. The EPA considered conducting the analysis at the lower iodine intake level of 50 µg/day, which represents approximately the 5th percentile of the NHANES distribution. However, at 50 µg/day of iodide, the BBDR model predicts TSH levels that would be elevated to within the clinically hypothyroid range before exposure to any perchlorate[7] (TSH ranges

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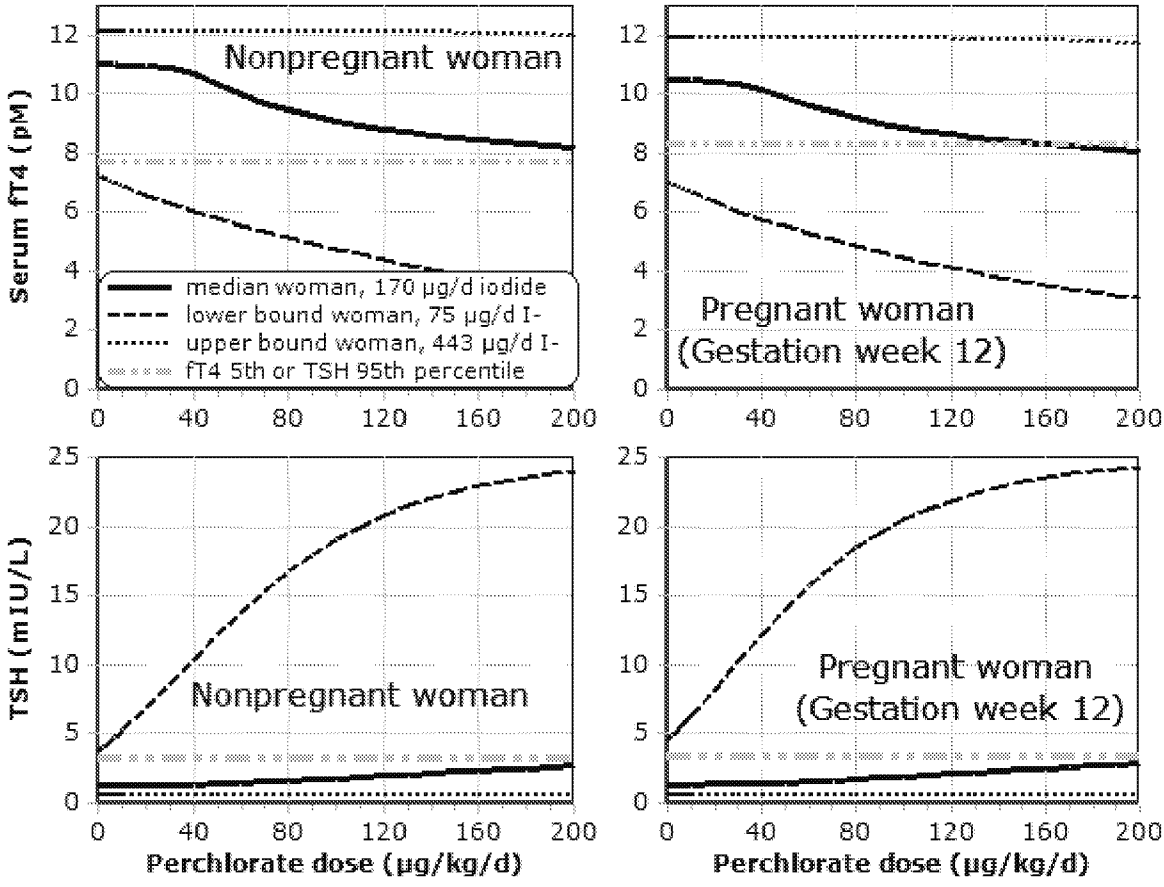
[7] For purposes of this analysis the EPA evaluated the American Thyroid Association's (ATA) 2017 recommendations for defining hypothyroidism [ADDIN EN.CITE <EndNote><Cite><Author>Alexander</Author><Year>2017</Year><RecNum>1895</RecNum><DisplayText>(Alexander et al., 2017)</DisplayText><record><rec-number>1895</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497970921">1895</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Alexander, E. K.</author><author>Pearce, E. N.</author><author>Brent, G. A.</author><author>Brown, R. S.</author><author>Chen, H.</author><author>Dosiou, C., </author><author>Sullivan, S.</author></authors></contributors><titles><title>2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>315-389</pages><volume>27</volume><number>3</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>]. Specifically, the ATA recommends: "in the pregnancy setting, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range." ATA goes on to state, in the absence of population- and trimester-specific references ranges defined by a provider's institute or laboratory, TSH reference ranges should be obtained from similar patient populations. From their recommended studies with trimester-specific data on a U.S. population, Lambert-Meserlian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lambert-

between 4.51 and 5.41 mIU/L at zero dose of perchlorate when evaluating GW 12 or GW 13). In contrast, at 75 µg/day iodine the BBDR-modeled concentrations of serum fT4 and TSH are significantly reduced from the population median but are still within the euthyroid range. This comports with the goal of evaluating perchlorate effects on neurodevelopment when starting with a population of pregnant women who are borderline hypothyroxinemic.

As described in Sections [REF _Ref488740188 \n \h] and [REF _Ref482958740 \r \h * MERGEFORMAT], the identified epidemiological literature led the EPA to select GW 12 and GW 13 for analysis. Results from the BBDR model output are subsequently summarized for these gestational weeks.

Messerlian</Author><Year>2008</Year><RecNum>100</RecNum><DisplayText>(2008)</DisplayText><record><rec-number>100</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1443808320">100</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lambert-Messerlian, Geralyn</author><author>McClain, Monica</author><author>Haddow, James E</author><author>Palomaki, Glenn E</author><author>Canick, Jacob A</author><author>Cleary-Goldman, Jane</author><author>Malone, Fergal D</author><author>Porter, T Flint</author><author>Nyberg, David A</author><author>Bernstein, Peter</author></authors></contributors><titles><title>First-and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First-and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study</title><secondary-title>American Journal of Obstetrics and Gynecology</secondary-title></titles><periodical><full-title>American journal of obstetrics and gynecology</full-title></periodical><pages>62-e1</pages><volume>199</volume><number>1</number><dates><year>2008</year></dates><publisher>Elsevier</publisher><isbn>0002-9378</isbn><urls></urls></record></Cite></EndNote>] is the largest U.S.-based population with a reference range upper bound of 3.37 mIU/L for the first trimester (and 3.35 mIU/L for the second trimester). Therefore, these values were used to compare to BBDR output TSH values in the first trimester (or second trimester in cases of GW 15 and GW 16) to determine the presence of hypothyroidism.

Figure [SEQ Figure * ARABIC]. Example Output from the BBDR Model[a]



[a] BBDR model simulations using parameter sets calibrated for median (black, solid curve), lower-bound (black, dashed curve), or upper-bound (black, dotted curve) fT4 levels, as described in Appendix A. TSH levels used for calibration were assumed to be inversely correlated with fT4; hence, the lower-bound level of TSH is associated with upper-bound fT4 and vice versa. Median and 90 µg/day percentile estimated iodine (I-) intake levels (170 and 443 µg/day, respectively) were used for simulations of median and upper-bound women. An iodine intake of 75 µg/day was used for the lower-bound woman, as described in the preceding text. Grey dash-dot lines show the 5th percentile of the estimated fT4 and upper bound for TSH, defining those boundaries of the euthyroid range.

Table [SEQ Table * ARABIC]. Predicted fT4 and TSH Concentrations at Various Doses of Perchlorate (µg/kg/day) at Specified Gestational Weeks for 170 µg/day Iodine Intake with pTSH = 0.398[a]

Perchlorate Dose (µg/kg/day)	fT4 (pmol/L) (% Change from 0 Dose)		TSH (mIU/L) (% Change from 0 Dose)	
	GW 12	GW 13	GW 12	GW 13
0	10.67	10.64	1.35	1.35
1	10.66	10.64	1.35	1.35
	(-0.04%)	(-0.05%)	(0.04%)	(0.04%)
2	10.66	10.63	1.35	1.35
	(-0.09%)	(-0.10%)	(0.07%)	(0.08%)
3	10.65	10.63	1.35	1.35
	(-0.13%)	(-0.14%)	(0.11%)	(0.12%)
4	10.65	10.62	1.35	1.35
	(-0.17%)	(-0.19%)	(0.15%)	(0.17%)
5	10.64	10.62	1.35	1.35
	(-0.22%)	(-0.24%)	(0.18%)	(0.21%)
10	10.62	10.59	1.35	1.36
	(-0.46%)	(-0.51%)	(0.39%)	(0.45%)

[a] Additional details can be found in Appendix A.

Percentages in the table may not mirror independent calculations due to rounding.

Table [SEQ Table * ARABIC]. Predicted fT4 and TSH Concentrations at Various Doses of Perchlorate (µg/kg/day) at Specified Gestational Weeks for 75 µg/day Iodine Intake with pTSH = 0.398[a]

Perchlorate Dose (µg/kg/day)	fT4 (pmol/L)	(% Change from 0 Dose)	TSH (mIU/L)	(% Change from 0 Dose)
	GW 12	GW 13	GW 12	GW 13
0	8.85	8.84	1.95	1.95
1	8.78	8.77	2.00	2.01
	(-0.80%)	(-0.79%)	(2.94%)	(2.92%)
2	8.71	8.71	2.06	2.07
	(-1.56%)	(-1.54%)	(5.96%)	(5.92%)
3	8.65	8.64	2.12	2.13
	(-2.29%)	(-2.26%)	(9.07%)	(9.01%)
4	8.59	8.58	2.18	2.19
	(-2.98%)	(-2.95%)	(12.26%)	(12.18%)
5	8.53	8.52	2.25	2.25
	(-3.64%)	(-3.60%)	(15.53%)	(15.44%)
10	8.27	8.27	2.59	2.60
	(-6.56%)	(-6.52%)	(33.06%)	(32.94%)

[a] Additional details can be found in Appendix A.

Percentages presented in the table may not mirror independent calculations due to rounding.

Table [SEQ Table * ARABIC]. Predicted fT4 and TSH Concentrations at Various Doses of Perchlorate (µg/kg/day) at Specified Gestational Weeks for 170 µg/day Iodine Intake with pTSH = 1[a]

Perchlorate Dose (µg/kg/day)	fT4 (pmol/L) (% Change from 0 Dose)		TSH (mIU/L) (% Change from 0 Dose)	
	GW 12	GW 13	GW 12	GW 13
0	10.67	10.64	1.35	1.35
1	10.66	10.64	1.35	1.35
	(-0.02%)	(-0.03%)	(0.02%)	(0.02%)
2	10.66	10.64	1.35	1.35
	(-0.05%)	(-0.05%)	(0.04%)	(0.05%)
3	10.66	10.63	1.35	1.35
	(-0.07%)	(-0.08%)	(0.06%)	(0.07%)
4	10.66	10.63	1.35	1.35
	(-0.10%)	(-0.11%)	(0.08%)	(0.09%)
5	10.65	10.63	1.35	1.35
	(-0.12%)	(-0.14%)	(0.10%)	(0.12%)
10	10.64	10.61	1.35	1.35
	(-0.25%)	(-0.28%)	(0.21%)	(0.24%)

[a] Additional details can be found in Appendix A.

Percentages in the table may not mirror independent calculations due to rounding.

Table [SEQ Table * ARABIC]. Predicted fT4 and TSH Concentrations at Various Doses of Perchlorate (µg/kg/day) at Specified Gestational Weeks for 75 µg/day Iodine Intake, pTSH = 1[a]

Perchlorate Dose (µg/kg/day)	fT4 (pmol/L)	(% Change from 0 Dose)	TSH (mIU/L)	(% Change from 0 Dose)
	GW 12	GW 13	GW 12	GW 13
0	8.85	8.84	1.95	1.95
1	8.81	8.80	1.98	1.99
	(-0.47%)	(-0.46%)	(1.68%)	(1.67%)
2	8.77	8.76	2.01	2.02
	(-0.92%)	(-0.91%)	(3.38%)	(3.36%)
3	8.73	8.72	2.05	2.05
	(-1.36%)	(-1.34%)	(5.12%)	(5.08%)
4	8.69	8.69	2.08	2.09
	(-1.78%)	(-1.76%)	(6.88%)	(6.83%)
5	8.66	8.65	2.11	2.12
	(-2.20%)	(-2.17%)	(8.67%)	(8.61%)
10	8.49	8.48	2.30	2.30
	(-4.11%)	(-4.08%)	(18.03%)	(17.93%)

[a] Additional details can be found in Appendix A.

Percentages in the table may not mirror independent calculations due to rounding.

[REF _Ref482950735 \h] shows that the BBDR model predicts very little difference in non-pregnant and first-trimester response to perchlorate. This likely occurs because the half-life of (organified)

iodine in the adult thyroid is several months (Dunn & Dunn, 2000, and Brabant et al., 1992, both as cited in Greer et al., 2002); hence the availability of thyroidal iodine in the first-trimester pregnant woman is determined to a very large extent by her nutrition and perchlorate exposure several years preceding pregnancy. Increased urinary clearance of both iodide and perchlorate during pregnancy, described by the model, have the conflicting effect of both reducing iodide availability in the mother and reducing perchlorate blood concentration, so these two components of pregnancy-related changes will cancel each other out to some extent. The similarity in dose-response also reflects the assumption that the small placental and fetal compartments, with the fetal thyroid only just becoming active at the end of the first trimester, will have very little effect on maternal anion and thyroid hormone concentrations, which led to the choice of a simplified model structure ([REF _Ref482868704 \h]). Further, there is little predicted change in the percentage drop in fT4 or percentage increase in TSH between gestational weeks due to perchlorate exposure, although baseline TSH and total T4 levels do vary significantly with gestation. However, there is a significant drop in fT4 and increase in TSH with decreased iodine intake in the absence of perchlorate exposure. Comparing the predicted fT4 and TSH levels at zero dose of perchlorate in [REF _Ref482951228 \h * MERGEFORMAT] (170 µg/day iodine intake) and [REF _Ref483557363 \h * MERGEFORMAT] (75 µg/day iodine intake) or [REF _Ref512496933 \h] and [REF _Ref512496934 \h] (a 56% drop in iodine intake from the median level), shows approximately a 16% to 17% drop in fT4 and approximately a 44% to 58% increase in TSH, depending on the gestational week of interest.

On the contrary, the BBDR model predictions for perchlorate's effect on fT4 are much less than the impact of decreased intake of iodine from 170 to 75 µg/day on fT4. For example, in the low-iodine intake individuals there is predicted to be about a 6% to 6.5% drop in fT4 with 10 µg/kg/day exposure to perchlorate. This result is consistent with the underlying Greer et al. (2002) data in human test subjects, which showed a NOAEL for perchlorate inhibition of radioiodide uptake by the thyroidal NIS of 7 µg/kg/day.

3.5 Uncertainties Associated with the BBDR Model

The BBDR model allows for the evaluation of perchlorate effects on circulating levels of fT4 based upon interaction with the thyroidal NIS before and during early pregnancy at various iodine intakes. Being biologically based, the model aims to simulate a complex physiological process that has been relatively well studied, the HPT axis. Interest in how perchlorate may perturb this system has spurred development of this modeling framework to predict such influences. Given the complexity of the model there can be uncertainties in many different aspects, ranging from structural and functional relationships to specific parameter values for early pregnancy. McLanahan et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>McLanahan</Author><Year>2009</Year><RecNum>248</RecNum><DisplayText>(2009)</DisplayText><record><rec-number>248</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468416019">248</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>McLanahan, E</author><author>Andersen, M. E.</author><author>Campbell, J. L.</author><author>Fisher, J. W.</author></authors></contributors><auth-address>Department of Environmental Health Sciences, University of Georgia, Athens, Georgia 30602-2102, USA.</auth-address><titles><title>Competitive inhibition of thyroidal uptake of dietary iodide by perchlorate does not describe perturbations in rat serum total T4 and TSH</title><secondary-title>Environmental Health Perspectives</secondary-

title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>731-8</pages><volume>117</volume><number>5</number><edition>2009/05/30</edition><keywords><keyword>Animals</keyword><keyword>Biological Transport/ drug effects</keyword><keyword>Iodides/ metabolism</keyword><keyword>Male</keyword><keyword>Perchlorates/ toxicity</keyword><keyword>Rats</keyword><keyword>Thyroid Gland/ drug effects/ metabolism</keyword><keyword>Thyrotropin/ blood</keyword><keyword>Thyroxine/ blood</keyword><keyword>Water Pollutants, Chemical/ toxicity</keyword></keywords><dates><year>2009</year><pub-dates><date>May</date></pub-dates></dates><isbn>1552-9924 (Electronic)
0091-6765 (Linking)</isbn><accession-num>19479014</accession-num><urls></urls><custom2>2685834</custom2><electronic-resource-num>10.1289/ehp.0800111</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] examined an earlier version of the model against data in rats exposed to high-dose perchlorate with the conclusion that the model under-predicted the degree of T4 decline and TSH rise. Given differences across species in thyroid storage of iodide and set points, and the effects of high versus lower dose perchlorate, the previous validation effort does not necessarily reflect on the predictive capacity of the current model. However, it does highlight the lack of useful calibration and validation data for this BBDR modeling effort.

On the pharmacokinetic side of the model, the submodels for iodide and perchlorate have been extensively developed and revised in the past (Merrill et al., 2005; Clewell et al., [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Clewell</Author><Year>2007</Year><RecNum>611</RecNum><DisplayText>(2007)</DisplayText><record><rec-number>611</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206428">611</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Clewell, R. A.</author><author>Merrill, E. A.</author><author>Gearhart, J. M.</author><author>Robinson, P. J.</author><author>Sterner, T. R.</author><author>Mattie, D. R.</author><author>Clewell, H. J.</author></authors></contributors><titles><title>Perchlorate and radioiodide kinetics across life stages in the human: using PBPK models to predict dosimetry and thyroid inhibition and sensitive subpopulations based on developmental stage</title><secondary-title>Journal of Toxicology and Environmental Health, Part A: Current Issues</secondary-title><alt-title>J Toxicol Environ Health A</alt-title><short-title>Journal of Toxicology and Environmental Health, Part A: Current Issues</short-title></titles><periodical><full-title>Journal of Toxicology and Environmental Health, Part A: Current Issues</full-title></periodical><alt-periodical><full-title>J Toxicol Environ Health A</full-title></alt-periodical><pages>408-428</pages><volume>70</volume><number>5</number><dates><year>2007</year></dates><isbn>ISSN 1528-7394</isbn><label>756734</label><urls><related-urls><url>http://dx.doi.org/10.1080/15287390600755216</url></related-urls></urls><electronic-resource-num>10.1080/15287390600755216</electronic-resource-num><language>English</language></record></Cite></EndNote>]; Lumen et al., 2013), although, as pointed out in McLanahan, White, Flowers, & Schlosser [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>McLanahan</Author><Year>2014</Year><RecNum>255</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>255</rec-number><foreign-keys><key

app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468516804">255</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>McLanahan, E</author><author>White, Paul</author><author>Flowers, Lynn</author><author>Schlosser, Paul M.</author></authors></contributors><titles><title>The use of PBPK models to inform human health risk assessment: Case study on perchlorate and radioiodide human lifestage models</title><secondary-title>Risk Analysis</secondary-title></titles><periodical><full-title>Risk Analysis</full-title></periodical><pages>356-366</pages><volume>34</volume><number>2</number><keywords><keyword>Human</keyword><keyword>PBPK model</keyword><keyword>perchlorate</keyword><keyword>radioiodide</keyword><keyword>risk assessment</keyword></keywords><dates><year>2014</year></dates><isbn>1539-6924</isbn><urls><related-urls><url><style face="underline" font="default" size="100%">http://dx.doi.org/10.1111/risa.12101</style></url></related-urls></urls><electronic-resource-num>10.1111/risa.12101</electronic-resource-num></record></Cite></EndNote>], there are very few calibration data for perchlorate kinetics in humans, particularly at the life stage of interest. This may be of particular importance given that available biomarker data to relate perchlorate external dose to internal serum concentration are highly variable and uncertain. For example, the Lumen et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Year>2013</Year><RecNum>107</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>107</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1450367396">107</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lumen, A.</author><author>Mattie, D.R.</author><author>Fisher, J.W.</author></authors></contributors><titles><title>Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model</title><secondary-title>Toxicological Sciences</secondary-title></titles><periodical><full-title>Toxicological Sciences</full-title></periodical><pages>320-341</pages><volume>133</volume><number>2</number><section>320</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1093/toxsci/kft078</electronic-resource-num></record></Cite></EndNote>] model was based on pregnant women living in a Chilean city with high levels of perchlorate in drinking water (Telléz Telléz et al., 2005). In that study, the standard deviation of the concentration of perchlorate in urine was similar to, or in one instance, greater than the mean urinary perchlorate concentration, indicating extreme variability. Furthermore, data used in the calibration from the Chilean city in Telléz Telléz et al. (2005) did not reflect a low-iodine intake population. Urinary iodide for the 37 subjects at the second pre-natal visit was, on average, 217 μg/L, with a standard deviation of 109 μg/L. Other toxicokinetic factors that may affect the concentration of perchlorate at the thyroidal NIS include the extent of protein binding, the perchlorate urinary excretion rate, and the partitioning into non-thyroidal compartments (i.e., the ROB compartment). However, of these three, only perchlorate urinary clearance affects the long-term average concentration of perchlorate at the thyroidal NIS predicted by the BBDR model, and given the half-life of iodine in the thyroid, it is this long-term average that determines the effect on thyroid hormone levels.

At steady state, or under long-term continuous exposure conditions, the (average) free concentration of perchlorate in plasma is independent of the fraction bound to protein. An increase in the concentration of binding proteins will result in a temporary decrease in the free perchlorate

concentration, resulting in a lower clearance rate to urine. Due to the lower clearance, there will then be an increase in total blood perchlorate concentration over a relatively short time (since exposure is ongoing) with urine clearance increasing in proportion to the free concentration and the amount bound to proteins also increasing, until steady state is again achieved with the free concentration returning to the same level as before the change in plasma proteins. The amount bound to proteins will then be increased in proportion to the increase in binding protein concentration. Likewise, a drop in binding proteins will cause a short-term increase in free perchlorate concentration, but this concentration will quickly return to the same steady-state level as before the protein level change as the amount bound to protein declines. Since such short-term fluctuations have minimal impact on the organified iodide in the thyroid, they are not significant to the overall dose-response.

There is some uncertainty due to the assumption that the concentration (and accumulation) of iodide and thyroid hormones in the placenta and fetus, and fetal metabolism of thyroid hormones, is not significantly different from the rest of the maternal body. For example, if the fetus and placenta are 2% of total maternal BW at a given point in gestation, and the amount of iodide accumulation or T4 metabolism in them is actually twice the average for the rest of the mother's body, the impact of neglecting that difference would only be a change of 2% in predicted maternal concentrations. The total rate of iodide accumulation or T4 metabolism in the fetus (not the rate per kg fetal BW) would have to be a significant fraction of the total maternal ingestion rate for iodine, or total maternal T4 metabolism and clearance, in order for the differences in the fetus to directly impact the maternal levels. (The model already accounts for the effects of hCG and changes in maternal physiology.) Hence the uncertainty from not including explicit placental and fetal compartments is determined by the uncertainty in the assumption that iodide accumulation and thyroid hormone metabolism are limited in early gestation.

The effect of the interaction between perchlorate and thiocyanate on thyroid hormone status seen in two epidemiology studies (Steinmaus et al., 2007; 2013) has been assumed to be due to a combined inhibitory effect on the NIS, but thiocyanate is also a competitive substrate for the thyroid peroxidase, a mechanism independent of perchlorate. While the BBDR model does not explicitly consider other goitrogens (e.g., thiocyanate, nitrate), simulating results for a mother with low iodine intake and low baseline fT4 may help to address the sensitivity of individuals with high exposures to other goitrogens.

The composite partition coefficient for perchlorate in ROB of 0.558 is considerably higher than that for iodide (0.243). Both perchlorate and iodide are subject to NIS-mediated uptake into mammary glands and skin, which is accounted for in the relevant partition coefficients. The higher PC for perchlorate (80% increase in perchlorate ROB coefficient) reflects the higher ratio of $Vmax/K_m$ for NIS-mediated transport into mammary glands and skin for perchlorate versus iodide. The BBDR model assumes this type of distributional impact of NIS uptake is plausible; however, it has not been evaluated using empirical data. But as noted above, this distribution will not impact the long-term average free serum concentration of perchlorate, which determines the effect on thyroid hormones.

A key pharmacokinetic factor is the perchlorate renal elimination rate, which is an influential parameter in the fitting procedure of Lumen et al. (2013), who attempted to match BBDR model predictions to biomarker measurements in pregnant Chilean women. However, that estimation assumed that perchlorate exposure was only in drinking water, with none coming from diet. When exposure is significantly under-estimated, a low level of urinary clearance would be required to match an observed serum concentration since the rate of absorption into the body is under-estimated. The

current modeling effort for early pregnancy uses an excretion rate that is more than twice that of the third-trimester Lumen et al. (2013) model. Merrill et al. (2005) estimated a urinary excretion rate (0.11 L/hr/kg$^{0.75}$) that is similar to what is used presently to represent the non-pregnant state, and this was based upon mean urinary perchlorate concentrations measured in the Greer et al. (2002) study. Evaluation of the variability in perchlorate urinary excretion in available human datasets is presented in Appendix A.

Toxicodynamic aspects such as competitive inhibition at the NIS, depletion of iodide stores under different iodine intake levels and physiological states, and the ability of the TSH feedback loop to compensate for perturbations in thyroid function each have their own uncertain features. A recent version of the BBDR model recalibrated for greater perchlorate affinity of the NIS (Schlosser, 2016) was able to simulate the dose-response for perchlorate's effect on radioiodide uptake seen in Greer et al. (2002). That correspondence builds confidence in the BBDR model's ability to simulate current data informing the user of perchlorate toxicokinetics and toxicodynamics in humans. However, the Greer et al. (2002) study was short-term, and did not evaluate the iodine intake status, smoking status, or intake of other goitrogens in volunteers, which may affect the ability to detect low-level perchlorate effects in population studies. Greer et al. (2002) used subjects' radioiodide uptake data as their own control, implicitly assuming that the impact of these other factors did not change over the weeks during which the study was conducted. The degree to which there is inter-individual variation in NIS structure and/or regulation contributing to variance across the population in the impact of perchlorate exposure on thyroid function is currently unknown.

Data for perchlorate effects on circulating hormone levels that might be used for model evaluation are very limited. Clinical toxicology and occupational studies in high-dose subjects showing minimal changes in thyroid hormone levels (Braverman, 2007) are discordant with general population epidemiology studies at much lower exposures that show associations between urinary perchlorate, TSH increases, and T4 (or fT4) decreases [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Given the limited data available for model evaluation, perchlorate toxicokinetics and toxicodynamics in pregnancy remain a source of uncertainty. This could impact the resulting fT4 predictions of neurodevelopmental effects. As an example, a comparison analysis of the BBDR model to predicted fT4 and TSH changes using the epidemiology literature (i.e., Steinmaus et al., 2016) is provided in Appendix B. This analysis used Steinmaus et al. (2016) to evaluate the relationship between perchlorate exposure and fT4 and TSH. When considering the median iodine intake, the changes predicted by the BBDR model for TSH are smaller than that predicted by Steinmaus et al. (2016), even when compared to the predictions based on the lower beta estimate from the 95% confidence interval (CI). However, when comparing the BBDR model's low-iodine TSH changes to those predicted by Steinmaus et al. (2016), they are closer in magnitude to the lower effect estimates and steadily increase to greater predicted changes as doses increase. In evaluating the results for fT4, in all instances the BBDR model predicts a smaller change than that projected by the Steinmaus et al. (2016) slope. The closest match, especially at lower perchlorate doses, is between the low-iodine runs of the BBDR model and the low estimate of the Steinmaus et al. (2016) slope. In addition, an approach to assess changes in IQ as a result of changes in perchlorate exposure using Steinmaus et al. (2016) is provided in Appendix C.

Incorporation of the TSH feedback loop into the model introduces other uncertainties. This is because, as discussed in Fitzgerald and Bean [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Year>2016</Year><RecNum>1876</RecNum><DisplayText>(2016)</Display

Text><record><rec-number>1876</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495213070">1876</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fitzgerald, S. P.</author><author>Bean, N. G.</author></authors></contributors><auth-address>Department of Internal Medicine and Department of Endocrinology, The Royal Adelaide Hospital, Adelaide, SA 5000, Australia; School of Medicine, The University of Adelaide, Adelaide, SA 5005, Australia.
School of Mathematical Sciences, The University of Adelaide, Adelaide, SA 5005, Australia; ARC Centre of Excellence for Mathematical and Statistical Frontiers, The University of Adelaide, Adelaide, SA 5005, Australia.</auth-address><titles><title>The relationship between population T4/TSH set point data and T4/TSH physiology</title><secondary-title>Journal of Thyroid Research</secondary-title></titles><periodical><full-title>Journal of Thyroid Research</full-title></periodical><pages>6351473</pages><volume>2016</volume><edition>2016/04/29</edition><dates><year>2016</year></dates><isbn>2090-8067 (Print)</isbn><accession-num>27123359</accession-num><urls></urls><custom2>4830732</custom2><electronic-resource-num>10.1155/2016/6351473</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>], increasing TSH levels do not have a consistently predictable impact on T4 levels. Fitzgerald and Bean (2016, p. 1) conclude that their mathematically derived curves describing the T4 response to TSH imply "greater inter-individual variation in the positive thyroid T4 response to TSH than in the central inhibitory TSH response to T4." Additionally, Hadlow et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Hadlow</Author><Year>2013</Year><RecNum>893</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>893</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206433">893</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hadlow, N. C.</author><author>Rothacker, K. M.</author><author>Wardrop, R.</author><author>Brown, S. J.</author><author>Lim, E. M.</author><author>Walsh, J. P.</author></authors></contributors><titles><title>The relationship between TSH and free T_4 in a large population is complex and nonlinear and differs by age and sex</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title><alt-title>J Clin Endocrinol Metab</alt-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><alt-periodical><full-title>J Clin Endocrinol Metab</full-title></alt-periodical><pages>2936-2943</pages><volume>98</volume><number>7</number><dates><year>2013</year></dates><isbn>ISSN 0021-972X
EISSN 1945-7197</isbn><label>3645386</label><urls><related-urls><url>http://dx.doi.org/10.1210/jc.2012-4223</url></related-urls></urls><electronic-resource-num>10.1210/jc.2012-4223</electronic-resource-num><language>English</language></record></Cite></EndNote>] demonstrated that the relationship between TSH and T4, while a consistently decreasing function, is variable across the population with factors such as genetics, subclinical thyroid disease, age, and gender contributing to this variability. Thus, the ability of the thyroid to respond after perturbation by perchlorate varies across the population. Further, the association between perchlorate and diminished T4 in the face of elevated TSH (Steinmaus et al., 2013; Steinmaus et al., 2007; Blount et al., 2005) suggests that certain segments of the population will have a limited ability to respond to perturbations through the TSH feedback mechanism. The reason is that some segments of the population have increased NIS inhibition due to other exposures (e.g., smokers) or increased perchlorate inhibition of the NIS because of low iodine intake. The strength of the TSH stimulatory effect is varied in model

predictions to account for such variability. The results in [REF _Ref482951228 \h] and [REF _Ref483557363 \h], for example, are from assuming pTSH = 0.398 (i.e., a stimulatory effect ~ 60% lower than pTSH = 1, results for which are presented in [REF _Ref512496933 \h] and [REF _Ref512496934 \h]) or direct proportionality, which otherwise appears to fit population median data reasonably well. Using either the weak or a stronger stimulatory term, the feedback does not maintain fT4 concentration exactly at the set point or target. Any exposure to perchlorate is predicted to reduce fT4 to some extent. The TSH feedback only reduces the dose-response compared to what is predicted without the term.

As mentioned above, the potential for perchlorate to interact with other goitrogens has been documented with respect to thiocyanate and tobacco smoking [ADDIN EN.CITE ADDIN EN.CITE.DATA]. As in the case with the low-iodide analysis of Blount et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Blount</Author><Year>2006</Year><RecNum>224</RecNum><DisplayText>(2006)</DisplayText><record><rec-number>224</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468246110">224</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Blount, B. C.</author><author>Pirkle, J. L.</author><author>Osterloh, J. D.</author><author>Valentin-Blasini, L.</author><author>Caldwell, K. L.</author></authors></contributors><titles><title>Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>1865-71</pages><volume>114</volume><number>12</number><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>], the interaction with thiocyanate was most evident in a nested design in which the vulnerable population of smokers could be evaluated separately from the remainder of the population [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Since data used in the calibration of the BBDR model were taken from NHANES 2007-12, with exclusion only for frank thyroid disease or medical treatment, they are presumed to be representative of the U.S. population as a whole. Since the NHANES data are also used to estimate overall exposure of the U.S. population to other goitrogens, the degree to which these may not reflect actual population exposure would point to an underlying problem in the NHANES sampling. The use of these data in the calibration of baseline thyroid hormone status effectively means that the predicted perchlorate dose-response is additive to the effect of existing exposure to other goitrogens in the NHANES 2007-12 population. Currently, the vulnerability introduced by other goitrogens' interactions with perchlorate at the NIS or on fT4 population distributions remains a source of uncertainty that could impact the resulting fT4 predictions of neurodevelopmental effects. The current BBDR model and analysis assume that exposures to perchlorate and other goitrogens vary independently in the population and that the effects are additive.

Investigation of the effect of perchlorate on iodine transport by the NIS *in vitro* [ADDIN EN.CITE <EndNote><Cite><Author>Kosugi</Author><Year>1996</Year><RecNum>280</RecNum><DisplayText>(Kosugi et al., 1996)</DisplayText><record><rec-number>280</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468526353">280</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kosugi, S.</author><author>Sasaki,

N.</author><author>Hai, N.</author><author>Sugawa, H.</author><author>Aoki, N.</author><author>Shigemasa, C.</author><author>Mori, T.</author><author>Yoshida, A.</author></authors></contributors><auth-address>Department of Laboratory Medicine, Kyoto University School of Medicine, Japan. kosugi@kuhp.kyto.u.ac.jp</auth-address><titles><title>Establishment and characterization of a Chinese hamster ovary cell line, CHO-4J, stably expressing a number of Na+/I- symporters</title><secondary-title>Biochemical and Biophysical Research Communications</secondary-title></titles><periodical><full-title>Biochemical and Biophysical Research Communications</full-title></periodical><pages>94-101</pages><volume>227</volume><number>1</number><edition>1996/10/03</edition><keywords><keyword>Animals</keyword><keyword>CHO Cells</keyword><keyword>Carrier Proteins/genetics/metabolism</keyword><keyword>Cell Line</keyword><keyword>Cloning, Molecular</keyword><keyword>Cricetinae</keyword><keyword>Ion Transport</keyword><keyword>Kinetics</keyword><keyword>Membrane Potentials</keyword><keyword>Membrane Proteins/genetics/metabolism</keyword><keyword>Rats</keyword><keyword>Symporters</keyword></keywords><dates><year>1996</year><pub-dates><date>Oct 3</date></pub-dates></dates><isbn>0006-291X (Print)
0006-291X (Linking)</isbn><accession-num>8858109</accession-num><urls></urls><electronic-resource-num>10.1006/bbrc.1996.1473</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>] and revised mathematical analysis by Schlosser (2016) indicate that this effect is consistent with classical competitive inhibition of the transporter. An equation describing this competitive inhibition is provided in Appendix A, Section 1.2.2. Based on this mechanism, and the simple pharmacokinetics of perchlorate (no metabolism, ~ 100% urinary excretion), it is assumed that there is minimal additional uncertainty in extrapolating the effect of perchlorate on iodide uptake downward from the middle perchlorate exposure levels used by Greer et al. (2002) (i.e., 20 and 100 µg/kg/day) to lower exposure levels relevant to MCLG derivation and/or human environmental exposures. The various uncertainties discussed above and in Appendix A do apply to low-dose extrapolation, but based on this mechanistic understanding there should be no magnification of uncertainty at low doses. The model is likely to become more uncertain when extrapolating to higher exposure levels, where mechanisms not included in the model may become active.

Lastly, the potential for perchlorate to interact with pre-existing thyroidal diseases and conditions is a source of uncertainty. The BBDR model presented here is intended to describe an otherwise healthy (euthyroid) woman during the period extending from several years before pregnancy through gestational week 16. Because it assumes euthyroid status, it does not, for example, address thyroiditis, which is caused by the production of thyroid autoantibodies (e.g., Hashimoto's disease) and is a common condition that may involve impaired iodide uptake across the NIS and in some individuals may result in reduced production of T4 [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The ATSDR Toxicological Profile for Perchlorate [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Year>2008</Year><RecNum>115</RecNum><DisplayText>(2008)</DisplayText><record><rec-number>115</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1465914059">115</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>ATSDR</author></authors></contributors><titles><title>Toxicological profile for perchlorates</title></titles><dates><year>2008</year></dates><pub-location>Atlanta, GA</pub-location><publisher>U.S. Department of Health and Human

Services</publisher><urls></urls></record></Cite></EndNote>] states that individuals with Hashimoto's disease and exposure to perchlorate have relatively poor thyroid function. To the extent that such conditions or pre-conditions cause additional interference with iodide uptake and deplete colloidal stores of iodide, this may set the stage for a toxicant-disease interaction with perchlorate that would constitute an added vulnerability and uncertainty consideration.

4. Deriving a Distribution of Thyroid Hormone Levels from the BBDR Model Output

While the BBDR model can be calibrated to match specific percentiles of the population, the distributions in the underlying parameters required to predict the distribution of thyroid hormone levels have not been determined. Therefore, in order to predict the impact of perchlorate exposure on the population distribution of fT4 (i.e., on the population fraction of hypothyroxinemic individuals; those with fT4 below the reference range and with TSH in the normal range), the EPA estimated a distribution for fT4 plasma concentrations around the median modeled values while accounting for the effects of perchlorate and iodine. This section describes the process of estimating these distributions.

4.1 Evaluation of Distributional Shape and Derivation of the Geometric Standard Deviation

Results from the literature review (see Section [REF _Ref488161860 \n \h]) suggest that it would be most useful to estimate distributions around the BBDR model output for GWs 12 and 13. Furthermore, this review suggested that it would be most useful to concentrate on fT4 rather than other thyroid hormones given maternal fT4 has the strongest relationship with neurodevelopmental outcomes (Korevaar et al., 2016; Pop et al., 1999, 2003; Finken et al., 2013). To develop population distributions for fT4 concentrations around the BBDR-estimated median fT4 values, the EPA evaluated the fT4 data from the studies that were used to calibrate the BBDR model (see Figure A-33 in Appendix A). Only one study provided distributional data for GW 13 fT4 [ADDIN EN.CITE <EndNote><Cite><Author>Männistö</Author><Year>2011</Year><RecNum>1206</RecNum><DisplayText>(Männistö et al., 2011)</DisplayText><record><rec-number>1206</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206438">1206</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Männistö, T.</author><author>Surcel, H. M.</author><author>Ruokonen, A.</author><author>Vääräsmäki, M.</author><author>Pouta, A.</author><author>Bloigu, A.</author><author>Järvelin, M. R.</author><author>Hartikainen, A. L.</author><author>Suvanto, E.</author></authors></contributors><titles><title>Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population</title><secondary-title>Thyroid</secondary-title><alt-title>Thyroid</alt-title></titles><periodical><full-title>Thyroid</full-title></periodical><alt-periodical><full-title>Thyroid</full-title></alt-periodical><pages>291-298</pages><volume>21</volume><number>3</number><dates><year>2011</year></dates><isbn>ISSN 1050-7256
EISSN 1557-9077</isbn><accession-num>21254924</accession-num><label>3590036</label><urls><related-urls><url>http://dx.doi.org/10.1089/thy.2010.0337</url></related-urls></urls><electronic-resource-num>10.1089/thy.2010.0337</electronic-resource-num><language>English</language></record></Cite></EndNote>], so GW 12 data were used to estimate distributional parameters for both gestational weeks. Specifically, Li et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Li</Author><Year>2014</Year><RecNum>342</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>342</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495025557">342</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Li, C.

</author><author>Shan, Z. </author><author>Mao, J.</author><author>et al.,</author></authors></contributors><titles><title>Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women?</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>73-79</pages><volume>99</volume><number>1</number><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>], Männistö et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2lq6ckhvho","properties":{"formattedCitation":"(2011)","plainCitation":"(2011)"},"citationItems":[{"id":920,"uris":["http://zotero.org/groups/945096/items/UAUDN6QU"],"uri":["http://zotero.org/groups/945096/items/UAUDN6QU"],"itemData":{"id":920,"type":"article-journal","title":"Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population","container-title":"Thyroid","page":"291-298","volume":"21","issue":"3","author":[{"family":"Männistö","given":"Tuija"},{"family":"Surcel","given":"Heljä-Marja"},{"family":"Ruokonen","given":"Aimo"},{"family":"Vääräsmäki","given":"Marja"},{"family":"Pouta","given":"Anneli"},{"family":"Bloigu","given":"Aini"},{"family":"Järvelin","given":"Marjo-Riitta"},{"family":"Hartikainen","given":"Anna-Liisa"},{"family":"Suvanto","given":"Eila"}],"issued":{"date-parts":[["2011"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}], and Zhang et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Zhang</Author><Year>2016</Year><RecNum>1864</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>1864</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206449">1864</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhang, X.</author><author>Yao, B.</author><author>Li, C.</author><author>Mao, J.</author><author>Wang, W.</author><author>Xie, X.</author><author>Teng, X.</author><author>Han, C.</author><author>Zhou, W.</author><author>Li, C.</author><author>Xu, B.</author><author>Bi, L.</author><author>Meng, T.</author><author>Du, J.</author><author>Zhang, S.</author><author>Gao, Z.</author><author>Yang, L.</author><author>Fan, C.</author><author>Teng, W.</author><author>Shan, Z.</author></authors></contributors><titles><title>Reference intervals of thyroid function during pregnancy: self-sequential longitudinal study versus cross-sectional study</title><secondary-title>Thyroid</secondary-title><alt-title>Thyroid</alt-title></titles><periodical><full-title>Thyroid</full-title></periodical><alt-periodical><full-title>Thyroid</full-title></alt-periodical><pages>1786-1793</pages><volume>26</volume><number>12</number><dates><year>2016</year></dates><isbn>ISSN 1050-7256
EISSN 1557-9077</isbn><label>3616173</label><urls><related-urls><url>http://dx.doi.org/10.1089/thy.2016.0002</url></related-urls></urls><electronic-resource-num>10.1089/thy.2016.0002</electronic-resource-num><language>English</language></record></Cite></EndNote>] were evaluated for GW 12 and GW 13 ([REF _Ref521509844 \h]).

All of the examined study data demonstrated a positive skew, and overall the lognormal function demonstrated a better fit than a normal distribution. Despite this, the available study data only accounted for variation due to gestational week, and did not account for variation in perchlorate and

iodine intake in the measured populations. Because perchlorate and iodine can affect fT4 levels, and this relationship produced the estimated median BBDR values, the distribution around values estimated by the model from perchlorate and iodine intake should account for a small reduction in variation due to the effect of perchlorate and iodine intake. Additionally, as iodine has a demonstrated lognormal distribution with strong right skew (e.g., Blount et al., 2007), and is predicted to have a stronger effect on fT4 than perchlorate (see Section 3), the EPA assumed the error around predicted fT4 would likely be closer to normal than lognormal after accounting for perchlorate and iodine intake.

Standard deviations (SDs) were estimated accounting for gestational week using quantile data from each relevant study with the *get.norm.par()* function from package rriskDistributions in R [ADDIN EN.CITE
<EndNote><Cite><Author>Belgorodski</Author><Year>2017</Year><RecNum>1992</RecNum><DisplayText>(Belgorodski, Greiner, Tolksdorf, & Schueller, 2017; R Core Team, 2018)</DisplayText><record><rec-number>1992</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1525116259">1992</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>Belgorodski, Natalia </author><author>Greiner, Matthias </author><author>Tolksdorf, Kristin </author><author>Schueller, Katharina</author></authors></contributors><titles><title>rriskDistributions: Fitting distributions to given data or known quantiles. R package version 2.1.2.</title></titles><dates><year>2017</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">https://CRAN.R-project.org/package=rriskDistributions</style></url></related-urls></urls></record></Cite><Cite><Author>R Core Team</Author><Year>2018</Year><RecNum>1993</RecNum><record><rec-number>1993</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1525116307">1993</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>R Core Team,</author></authors></contributors><titles><title>R: A language and environment for statistical computing. R Foundation for Statistical Computing</title></titles><dates><year>2018</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">https://www.R-project.org/</style></url></related-urls></urls></record></Cite></EndNote>]. SDs were back-calculated based on all available centile data for fT4, resulting in a single SD from each study. The EPA then estimated a combined SD for GW 12 studies and applied it to both GW 12 and GW 13. This was done because the only available GW 13 data were from Männistö et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2lq6ckhvho","properties":{"formattedCitation":"(2011)","plainCitation":"(2011)"},"citationItems":[{"id":920,"uris":["http://zotero.org/groups/945096/items/UAUDN6QU"],"uri":["http://zotero.org/groups/945096/items/UAUDN6QU"],"itemData":{"id":920,"type":"article-journal","title":"Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population","container-title":"Thyroid","page":"291-298","volume":"21","issue":"3","author":[{"family":"Männistö","given":"Tuija"},{"family":"Surcel","given":"Heljä-Marja"},{"family":"Ruokonen","given":"Aimo"},{"family":"Vääräsmäki","given":"Marja"},{"family":"Pouta","given":"Anneli"},{"family":"Bloigu","given":"Aini"},{"family":"Järvelin","given":"Marjo-Riitta"},{"family":"Hartikainen","given":"Anna-

Liisa"},{"family":"Suvanto","given":"Eila"}],"issued":{"date-parts":[["2011"]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] that also contained GW 12 data. This introduced unnecessary complications into the estimation of a combined SD using data from both gestational weeks, as the two different weeks had different sample sizes, and the SD of the GW 13 data fell within the range of SDs estimated from other studies with GW 12 fT4 data. As such, the EPA opted to only estimate a combined SD using data from GW 12.

The EPA used the *combinevar()* function from the *fishmethods* package (Nelson, 2017) to estimate combined variance weighted by sample size (Appendix D). This yielded a representative SD for GW 12 and GW 13 based on the relevant data from each study. These SDs were assumed to represent the median-iodine intake distribution, as this is what these studies were used for in model calibration. After estimating the combined SD, the EPA assumed a small reduction in variability would occur when further accounting for known iodide and perchlorate intakes. The EPA based the estimate of this reduction on results from Steinmaus et al. (2016). Steinmaus et al. (2016) incorporated both iodide and perchlorate measurements into a regression model describing thyroid hormone levels. The overall model described a large portion of the variance. While both iodide and perchlorate significantly affected fT4 values, the authors did not provide simple measures to allow an assessment of how much each of these contributed to the overall fit. As such, the EPA estimated that the combination of these intakes would be analogous to an R^2 of roughly 0.1, which would indicate a small to medium effect size. The EPA adjusted the standard deviation for this rough estimate as follows:

$$Adjusted\ SD = \sqrt[2]{(1 - R^2)} * Combined\ SD$$

While this method does not account for non-linearity in the effects of perchlorate and iodine intake, it does help to incorporate the model assumption that both iodine and perchlorate affect fT4 concentrations.

More information on these methods can be found in Appendix D.

Table [SEQ Table * ARABIC]. Estimated SDs, Sample Sizes, and Combined SDs Based on Data from Relevant Studies with fT4 Data from GW 12 and GW 13

Study - Gestational Week	Combined SD	Sample Size	Combined SD Raw Media Iodine Intake	Adjusted SD for Media Iodine and No Perchlorate	Adjusted SD for Low Iodine and No Perchlorate
Li et al. (2014) – Week 12	2.13	128	2.12	2.01	1.67
Männistö et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2lq6ckhvho","properties":{"formattedCitation":"(2011)","plainCitation":"(2011)"},"citationItems":[{"id":920,"uris":["http://zotero.org/groups/945096/items/UAUDN6QU"],"uri":["http://zotero.org/groups/945096/items/UAUDN6QU"],"itemData":{"id":920,"type":"article-journal","title":"Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population","container-title":"Thyroid","page":"291-298","volume":"21","issue":"3","author":[{"family":"Männistö","given":"Tuija"},{"family":"Surcel","given":"Heljä-Marja"},{"family":"Ruokonen","given":"Aimo"},{"family":"Vääräsmäki","given":"Marja"},{"family":"Pouta","given":"Anneli"},{"family":"Bloigu","given":"Aini"},{"family":"Järvelin","given":"Marjo-Riitta"},{"family":"Hartikainen","given":"Anna-Liisa"},{"family":"Suvanto","given":"Eila"}],"issued":{"date-parts":[["2011"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] – Week 12	2.19	454			

Study - Gestational Week	Combined SD	Sample Size	Combined SD Raw Media and lodine Intake	Adjusted SD for Media and lodine and No Perchlorate	Adjusted SD for Low lodine and No Perchlorate
Männistö et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2lq6ckhvho","properties":{"formattedCitation":"(2011)","plainCitation":"(2011)"},"citationItems":[{"id":920,"uris":["http://zotero.org/groups/945096/items/UAUDN6QU"],"uri":["http://zotero.org/groups/945096/items/UAUDN6QU"],"itemData":{"id":920,"type":"article-journal","title":"Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population","container-title":"Thyroid","page":"291-298","volume":"21","issue":"3","author":[{"family":"Männistö","given":"Tuija"},{"family":"Surcel","given":"Heljä-Marja"},{"family":"Ruokonen","given":"Aimo"},{"family":"Vääräsmäki","given":"Marja"},{"family":"Pouta","given":"Anneli"},{"family":"Bloigu","given":"Aini"},{"family":"Järvelin","given":"Marjo-Riitta"},{"family":"Hartikainen","given":"Anna-Liisa"},{"family":"Suvanto","given":"Eila"}],"issued":{"date-parts":[["2011"]]}},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] – Week 13	1.98	325			
Zhang et al. [ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2bolpmks7v","properties":{"formattedCitation":"(2016)","plainCitation":"(2016)"},"citationItems":[{"id":918,"uris":["http://zotero.org/groups/945096/items/HTDB3EVS"],"uri":["http://zotero.org/groups/945096/items/HTDB3EVS"],"itemData":{"id":918,"type":"article-journal","title":"Reference Intervals of Thyroid Function During Pregnancy: Self-Sequential Longitudinal Study Versus Cross-Sectional Study","container-title":"Thyroid","page":"1786-1793","volume":"26","issue":"12","source":"CrossRef","DOI":"10.1089/thy.2016.0002","ISSN":"1050-7256, 1557-9077","shortTitle":"Reference Intervals of Thyroid Function During	1.67	87			

Study - Gestational Week	Combined SD	Sample Size	Combined SD Raw Median Iodine Intake	Adjusted SD for Median Iodine and No Perchlorate	Adjusted SD for Low Iodine and No Perchlorate
Pregnancy","language":"en","author":[{"family":"Zhang","given":"Xiaomei"},{"family":"Yao","given":"Baoting"},{"family":"Li","given":"Chenyan"},{"family":"Mao","given":"Jinyuan"},{"family":"Wang","given":"Weiwei"},{"family":"Xie","given":"Xiaochen"},{"family":"Teng","given":"Xiaochun"},{"family":"Han","given":"Cheng"},{"family":"Zhou","given":"Weiwei"},{"family":"Li","given":"Chenyang"},{"family":"Xu","given":"Bin"},{"family":"Bi","given":"Lihua"},{"family":"Meng","given":"Tao"},{"family":"Du","given":"Jianling"},{"family":"Zhang","given":"Shaowei"},{"family":"Gao","given":"Zhengnan"},{"family":"Yang","given":"Liu"},{"family":"Fan","given":"Chenling"},{"family":"Teng","given":"Weiping"},{"family":"Shan","given":"Zhongyan"}],"issued":{"date-parts":[["2016",12]]},"suppress-author":true}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}] – Week 12					

4.2 Results of Estimating a Distribution around BBDR Median Output

The EPA used estimated SDs to predict distributions of fT4 around BBDR median fT4 estimates, based on particular levels of iodine sufficiency and doses of perchlorate. The *qnorm()* function from the *stats* package in R (R Core Team, 2018), which is analogous to the Microsoft® Excel norm.inv function described in Ginsberg et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ginsberg</Author><Year>2014</Year><RecNum>89</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>89</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

timestamp="1443721948">89</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ginsberg, G.</author><author>Sonawane, B.</author><author>Nath, R.</author><author>Lewandowski, P.</author></authors></contributors><titles><title>Methylmercury-induced inhibition of paraoxonase-1 (PON1) - Implications for cardiovascular risk</title><secondary-title>Journal of Toxicology and Environmental Health, Part A: Current Issues</secondary-title></titles><periodical><full-title>Journal of Toxicology and Environmental Health, Part A: Current Issues</full-title></periodical><pages>1004-1023</pages><volume>77</volume><number>17</number><section>1004</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1080/15287394.2014.919837</electronic-resource-num></record></Cite></EndNote>], was used for these predictions. [REF _Ref512860801 \h] and [REF _Ref512860806 \h] demonstrate fT4 distributions for various doses of perchlorate based on the EPA's calculated SDs for GW 12 and GW 13, respectively, for median iodine intake and low iodine intake assuming pTSH = 0.398. [REF _Ref512860812 \h] and [REF _Ref512860816 \h] demonstrate these results assuming pTSH = 1.

Table [SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 for GW 12 at 75 and 170 µg/day Iodine Intake at pTSH = 0.398 []

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)					
	2.5th	5th	10th	50th	95th	97.5th
Iodine Intake = 170 µg/day[a]						
0	6.72	7.36	8.09	10.67	13.97	14.61
1	6.72	7.35	8.08	10.66	13.97	14.60
2	6.71	7.35	8.08	10.66	13.97	14.60
3	6.71	7.34	8.07	10.65	13.96	14.60
4	6.70	7.34	8.07	10.65	13.96	14.59
5	6.70	7.33	8.06	10.64	13.95	14.59
10	6.67	7.31	8.04	10.62	13.93	14.56
Iodine Intake = 75 µg/day[b]						
0	5.58	6.11	6.71	8.85	11.60	12.12
1	5.51	6.04	6.64	8.78	11.52	12.05
2	5.44	5.97	6.57	8.71	11.46	11.98
3	5.38	5.90	6.51	8.65	11.39	11.92
4	5.32	5.84	6.45	8.59	11.33	11.86
5	5.26	5.78	6.39	8.53	11.27	11.80
10	5.00	5.53	6.13	8.27	11.01	11.54

[a] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a normal distribution with a SD = **2.01**.
[b] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a normal distribution with a SD = **1.67**.

Table [SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 for GW 13 at 75 and 170 µg/day Iodine Intake at pTSH = 0.398

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)					
	2.5th	5th	10th	50th	95th	97.5th
Iodine Intake = 170 µg/day[a]						
0	6.70	7.33	8.07	10.64	13.95	14.59
1	6.70	7.33	8.06	10.64	13.95	14.58
2	6.69	7.32	8.06	10.63	13.94	14.58
3	6.69	7.32	8.05	10.63	13.94	14.57
4	6.68	7.31	8.04	10.62	13.93	14.57
5	6.67	7.31	8.04	10.62	13.93	14.56
10	6.65	7.28	8.01	10.59	13.90	14.53
Iodine Intake = 75 µg/day[b]						
0	5.57	6.09	6.70	8.84	11.59	12.12
1	5.50	6.02	6.63	8.77	11.52	12.05
2	5.43	5.96	6.56	8.71	11.45	11.98
3	5.37	5.89	6.50	8.64	11.39	11.92
4	5.31	5.83	6.44	8.58	11.33	11.86
5	5.25	5.77	6.38	8.52	11.27	11.80
10	4.99	5.52	6.12	8.27	11.01	11.54

[a] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a normal distribution with a SD = **2.01**.

[b] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a normal distribution with a SD = **1.67**.

Table [SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 for GW 12 at 75 and 170 µg/day Iodine Intake at pTSH = 1

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)					
	2.5th	5th	10th	50th	95th	97.5th
Iodine Intake = 170 µg/day[a]						
0	6.72	7.36	8.09	10.67	13.97	14.61
1	6.72	7.35	8.09	10.66	13.97	14.61
2	6.72	7.35	8.08	10.66	13.97	14.60
3	6.72	7.35	8.08	10.66	13.97	14.60
4	6.71	7.35	8.08	10.66	13.96	14.60
5	6.71	7.34	8.07	10.65	13.96	14.60
10	6.70	7.33	8.06	10.64	13.95	14.58
Iodine Intake = 75 µg/day[b]						
0	5.58	6.11	6.71	8.85	11.60	12.12
1	5.54	6.06	6.67	8.81	11.55	12.08
2	5.50	6.02	6.63	8.77	11.51	12.04
3	5.46	5.99	6.59	8.73	11.48	12.00
4	5.42	5.95	6.55	8.69	11.44	11.96
5	5.39	5.91	6.52	8.66	11.40	11.93
10	5.22	5.74	6.35	8.49	11.23	11.76

[a] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a normal distribution with a SD = **2.01**.
[b] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a normal distribution with a SD = **1.67**.

Table [SEQ Table * ARABIC]. Summary of BBDR Model Results for fT4 for GW 13 at 75 and 170 µg/day Iodine Intake at pTSH = 1

Perchlorate Dose (µg/kg/day)	Percentile fT4 (pmol/L)					
	2.5th	5th	10th	50th	95th	97.5th
Iodine Intake = 170 µg/day[a]						
0	6.70	7.33	8.07	10.64	13.95	14.59
1	6.70	7.33	8.06	10.64	13.95	14.58
2	6.69	7.33	8.06	10.64	13.95	14.58
3	6.69	7.33	8.06	10.63	13.94	14.58
4	6.69	7.32	8.05	10.63	13.94	14.58
5	6.69	7.32	8.05	10.63	13.94	14.57
10	6.67	7.30	8.04	10.61	13.92	14.56
Iodine Intake = 75 µg/day[b]						
0	5.57	6.09	6.70	8.84	11.59	12.12
1	5.53	6.05	6.66	8.80	11.55	12.08
2	5.49	6.01	6.62	8.76	11.51	12.04
3	5.45	5.97	6.58	8.72	11.47	12.00
4	5.41	5.94	6.54	8.69	11.44	11.96
5	5.37	5.90	6.51	8.65	11.40	11.93
10	5.21	5.73	6.34	8.48	11.23	11.76

[a] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a normal distribution with a SD = **2.01**.
[b] 50th percentile is direct output from the BBDR model, additional percentile estimated by assuming a normal distribution with a SD = **1.67**.

4.3 Limitations and Uncertainties of Method

Although the lognormal distribution better describes the reported quantiles of fT4 in the manuscripts reviewed when accounting for gestational week, the EPA opted to assume a normal distribution. Departures from normality were small in the published quantile data (Appendix D, Figure D-1), and it was assumed that the distribution of error around values of fT4 accounting for perchlorate and iodine would even more closely approach a normal distribution. The primary limitation of this process is that very few published studies allowed for the estimation of the strength of the effects of perchlorate and iodine on fT4 levels, or the shape of the relationships. A rough estimate of the distribution is provided based on an assumption that the combination of accounting for iodide and perchlorate would provide a reduction in error analogous to an R^2 of 0.1. While the effects of perchlorate and iodide are non-linear, the EPA has no additional information that would allow for the further improvement of the estimation of the error distribution. The current method for estimating the error distribution avoids producing centile intervals that are likely to be wider than the true intervals.

5. Connecting Alterations in Thyroid Hormone Levels to Alterations in Neurodevelopment: Identification of Studies for Further Analysis

This section addresses the SAB recommendation to "identify literature and conduct analyses to support the model outputs for the downstream steps" [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Pages>27-28</Pages><DisplayText>(SAB, 2013, pp. 27-28)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>] from the BBDR's predicted changes in thyroid hormones. Specifically, this section presents the process by which literature was identified to complete the linkage between altered maternal T4 and fT4 (as predicted by the BBDR model) and adverse neurodevelopmental effects in offspring. Section [REF _Ref482275327 \r \h] presents the process used to identify the literature to support this approach. Sections [REF _Ref491075421 \n \h] and [REF _Ref482275344 \r \h] describe the literature search approach and results of the process used to identify relevant studies that can link the predictions of changes in fT4 from the BBDR model to incremental changes in neurodevelopment. Section [REF _Ref482275380 \r \h] presents results from the literature that are used to support an alternative proposed approach presented in Section [REF _Ref481160968 \r \h]: evaluating a shift in the proportion of the population that will fall below a hypothyroxinemic cut point, given exposure to perchlorate.

5.1 Searching the Published Literature

The available data for the second stage of the analysis come from epidemiological studies that evaluated maternal thyroid hormone levels in pregnancy and neurodevelopmental outcomes (these are not studies evaluating perchlorate exposure). Based on the recommendations of previous peer review panels, the EPA assumed that changes in thyroid hormone levels would be expected to lead to neurodevelopmental outcomes. For this reason, the EPA did not conduct a complete, systematic review of the body of literature on this topic. However, the EPA conducted a focused review of the published literature and identified epidemiological studies that examined thyroid hormone levels and neurodevelopmental outcomes.

The EPA conducted the literature searches in PubMed and Google Scholar focusing on epidemiologic studies that explicitly evaluated the association between maternal thyroid hormone T4 or fT4 levels and offspring neurodevelopment. A protocol was developed to identify and evaluate the studies located. Studies were categorized based on whether the analysis was based on a categorical or a continuous measure of thyroid hormones as they related to neurodevelopment, and then studies identified as potentially useful for further dose-response analysis went through a risk-of-bias (ROB) analysis. Search strings and categories are presented in [REF _Ref424292244 \h * MERGEFORMAT]. As depicted in this table, the endpoints included neurodevelopmental measures, autism spectrum disorder (ASD), and attention deficit/hyperactivity disorder (ADHD). These

categories were chosen as outcomes associated with alterations in thyroid hormone levels based on the 2013 SAB recommendations, CalEPA's *Public Health Goal for Perchlorate in Drinking Water* [ADDIN EN.CITE <EndNote><Cite><Author>CalEPA</Author><Year>2011</Year><RecNum>296</RecNum><DisplayText>(CalEPA, 2011)</DisplayText><record><rec-number>296</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1470937233">296</key></foreign-keys><ref-type name="Computer Program">9</ref-type><contributors><authors><author>CalEPA</author></authors></contributors><titles><title>Draft: Public health goal for perchlorate in drinking water</title></titles><dates><year>2011</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">https://oehha.ca.gov/media/downloads/water/public-health-goal/010711perchloratephg.pdf</style></url></related-urls></urls></record></Cite></EndNote>] and the National Research Council's *Health Implications of Perchlorate Ingestion* [ADDIN EN.CITE <EndNote><Cite><Author>NRC</Author><Year>2005</Year><RecNum>1332</RecNum><DisplayText>(NRC, 2005)</DisplayText><record><rec-number>1332</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1495206440">1332</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>NRC</author></authors></contributors><titles><title>Health implications of perchlorate ingestion</title></titles><dates><year>2005</year></dates><pub-location>Washington, DC</pub-location><publisher>National Academies Press</publisher><label>627612</label><urls><related-urls><url>http://www.nap.edu/catalog/11202.html</url></related-urls></urls><modified-date>National Research Council</modified-date></record></Cite></EndNote>].

Searches were restricted to studies published since 2000 to limit the results to the most recent science. Limiting studies to the past 17 years was supported by Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>1999</Year><RecNum>40</RecNum><DisplayText>(1999)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062208">40</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Kuijpens, J L</author><author>van Baar, A L</author><author>Verkerk, G</author><author>van Son, M M</author><author>de Vijlder, J J</author><author>Vulsma, T</author><author>Wiersinga, W M</author><author>Drexhage, H A</author><author>Vader, H L</author></authors></contributors><titles><title>Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>149-155</pages><volume>50</volume><section>149</section><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>] (this study was identified by SAB, 2013), who noted there were no studies evaluating the relationship between maternal thyroid hormone levels and infant neurodevelopment from iodine-sufficient populations prior to 1999. In addition, the SAB document [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-

keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>] was reviewed to confirm that the literature search captured all of the studies cited as potential references that evaluate the relationship between thyroid hormone and neurodevelopment [ADDIN EN.CITE <EndNote><Cite><Author>SAB</Author><Year>2013</Year><RecNum>50</RecNum><Prefix>e.g.`, pages 10`, 15`, and 28 of </Prefix><DisplayText>(e.g., pages 10, 15, and 28 of SAB, 2013)</DisplayText><record><rec-number>50</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437138201">50</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>SAB,</author></authors><secondary-authors><author>U.S. Environmental Protection Agency,</author></secondary-authors></contributors><titles><title>Advice on approaches to derive a maximum contaminant level goal for perchlorate. EPA-SAB-13-004</title></titles><dates><year>2013</year></dates><pub-location>Washington, DC</pub-location><urls></urls></record></Cite></EndNote>], including some that were published prior to 2000. Titles and abstracts of all studies were reviewed to determine if the study had pertinent information relating thyroid hormone levels, particularly T4 or fT4, and adverse neurodevelopmental outcomes. Further, to ensure all relevant papers were captured, recent review papers, including three systematic reviews (Fetene et al., 2018; Moog et al., 2017, Thompson et al., 2018) pertaining to altered maternal thyroid hormone levels and offspring neurodevelopment were also evaluated.[8]

Reviewing the Google Scholar and PubMed literature searches resulted in the identification of 59 studies that assessed the relationship between maternal thyroid hormone levels and neurodevelopmental outcomes in the offspring. Review of the SAB document identified six additional papers[9] to evaluate, and review of recent systematic reviews identified six additional papers[10] to evaluate. Therefore, a total of 71 studies that pertained to altered maternal thyroid hormone levels and offspring neurodevelopment were identified for evaluation.

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[8] Summary tables of the articles were evaluated. If a study was identified in these tables as containing information on hypothyroxinemia or fT4 and an assessment of neurodevelopment, it was further reviewed for potential relevance.

[9] Haddow et al. (1999); Man, Brown, and Serunian (1991); Pharoah, Connolly, Ekins, and Harding (1984); Pop et al. (1999); Velasco et al. (2009); Willoughby (2011).

[10] Brown et al. (2015); Ghassabian et al. (2011); Ghassabian et al. (2012); Kasatkina et al. (2006); Lazarus et al. (2012); Muñoz, Figueras, & Puig (2009).

Table [SEQ Table * ARABIC]. Summary of Search Strings Used

Search Category	Search Strings[a]
Endpoint: Neurodevelopment	• Neurodevelopment AND hypothyroxinemia[b] • "Neurodevelopmental effects" AND hypothyroxinemia[b] • Hypothyroxinemia AND behavior • Hypothyroxinemia AND behavior AND infant • Hypothyroxinemia AND thyroxine AND behavior AND infant • (Thyroxine OR T4 OR hypothyroxinemia) AND (neurodevelopment OR "mental ability" OR intelligence OR cognition OR cognitive OR motor OR language)
Endpoint: Attention Deficit/ Hyperactivity Disorder	• "Maternal hypothyroxinemia" AND thyroxine AND ADHD AND infant
Endpoint: Autism	• Hypothyroxinemia AND autism[b] • Hypothyroxinemia AND thyroxine AND autism AND infant

[a] Searches were restricted to studies published from 2000 to February 14, 2018.
[b] This search string resulted in more articles than the EPA could reasonably evaluate. Therefore, the search was constrained so that databases searched for those terms only in the title.

5.2 Approach to Locate Epidemiological Studies That Evaluated Maternal Thyroid Hormone Levels in Early Pregnancy and Neurodevelopmental Outcomes

To identify studies that linked incremental changes in maternal T4 or fT4 to incremental changes in offspring neurodevelopment (Step 2 in [REF _Ref417634154 \h]), the EPA assessed each of the 71 studies identified using a four-step approach. First, studies were identified that were not compatible with BBDR model results (see Section [REF _Ref517273217 \r \h]). Studies were then categorized depending on whether the analysis was based on a categorical or a continuous measure of thyroid hormones as they related to neurodevelopment (see Section [REF _Ref517273232 \r \h]). Studies with potential for further dose-response analysis were then evaluated using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) ROB tool (see Section [REF _Ref512802830 \r \h]). Lastly, the remaining papers were evaluated to determine if it would be feasible to use data from the paper in dose-response analysis (see Section [REF _Ref457207854 \r \h]).

Each step is described below.

5.2.1 Step 1. Identify Studies That Are Not Compatible with BBDR Model Results

First, studies were identified that are not compatible with BBDR model results to inform MCLG development. Specifically, studies were identified with the following features:

- The study design is not directly compatible with the BBDR model results. For example, if the study evaluated the impact of only neonatal thyroid hormones (i.e., at a potentially sensitive life stage), it cannot be used because the BBDR model is specific to early pregnancy. Further, if the study evaluates a population with an existing disease (i.e., hypothyroidism) that may have a different response to perchlorate compared to the euthyroid population, it was not considered compatible with BBDR model results. Additionally, if the study does not include

information on T4 or fT4, it does not assist in understanding the implications of the BBDR modeling results.

- The study does not have a population with an exposure window (i.e., when the thyroid hormone measurements are taken) that overlaps with the outputs for the BBDR model. Specifically, the study should evaluate thyroid hormone levels in pregnant mothers between conception and gestational week 16. The neurodevelopmental outcomes could be measured at any life stage.

Any studies identified in this step were categorized as Group 3.

5.2.2 Step 2. Categorize the Remaining Studies

The remaining studies were evaluated based on the analysis approach presented in the study. Studies were categorized based on the presence of an analysis that could inform how incremental changes in fT4 related to incremental changes in a neurodevelopmental outcome. Specifically:

- Studies that present any analyses based on a continuous measure of maternal thyroid hormone levels and subsequent offspring neurodevelopmental outcomes were placed into Group 1. These studies present data to inform an analysis that allows for an understanding of the impact of incremental changes in thyroid hormones and subsequent neurodevelopmental impacts.
- Studies that present analyses based only on categorical analyses of thyroid hormones (e.g., yes/no hypothyroxinemic) and subsequent neurodevelopmental effects were placed into Group 2.

Grouping of studies in this manner does not pertain to the quality of the data presented. Instead, it directly relates to the utility of the paper in informing a dose-response analysis as it pertains to evaluating the impact incremental changes in thyroid hormones and thus, potential incremental changes in neurodevelopment. Subsequently, very high quality papers that contributed significantly to the understanding of maternal thyroid hormones' impact on offspring neurodevelopment may be considered Group 2 or Group 3. This is simply because these papers do not allow for a quantitative understanding of the relationship between maternal thyroid hormone levels in early pregnancy and offspring neurodevelopment.

5.2.3 Step 3. Conduct Risk Of Bias (ROB) Evaluation of Group 1 Papers

A data quality analysis was conducted on each of the Group 1 papers as outlined in more detail in Appendix E. In summary, the ROB evaluation was based on the National Toxicology Program's 2015 *OHAT Risk of Bias Rating Tool for Human and Animal Studies* [ADDIN EN.CITE <EndNote><Cite><Author>National Toxicology Program</Author><Year>2015</Year><RecNum>1987</RecNum><DisplayText>(National Toxicology Program, 2015b)</DisplayText><record><rec-number>1987</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1525098556">1987</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>National Toxicology Program, </author></authors><secondary-authors><author>Office of Health Assessment and Translation (OHAT)</author></secondary-authors></contributors><titles><title>OHAT risk of bias rating tool for human and animal

studies</title></titles><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>] and its 2015 *Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration* [ADDIN EN.CITE <EndNote><Cite><Author>National Toxicology Program</Author><Year>2015</Year><RecNum>1988</RecNum><DisplayText>(National Toxicology Program, 2015a)</DisplayText><record><rec-number>1988</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1525098718">1988</key></foreign-keys><ref-type name="Government Document">46</ref-type><contributors><authors><author>National Toxicology Program,</author></authors><secondary-authors><author>OHAT</author></secondary-authors></contributors><titles><title>Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration</title></titles><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>]. Under this approach, a ROB was first assigned to rate each of five key components of a study, based on the following questions:

1. Did the study design or analysis account for important confounding and modifying variables?
2. Were outcome data complete without attrition or exclusion from analysis?
3. Can we be confident in the exposure characterization?
4. Can we be confident in the outcome assessment?
5. Were all measured outcomes reported?

Criteria for ranking studies on each question were adapted from the OHAT ROB rating tool and are displayed in full in Appendix E. Possible ROB ratings for each question were: definitely low, probably low, probably high, or definitely high ROB. For example, under outcome assessment, studies were rated as definitely low ROB if they used well-established methods to assess outcomes, followed all subjects for the same length of time, and provided evidence of blinding of outcome assessors.

Based on the five ROB rankings, each Group 1 study was assigned a further rating of overall study quality ranging from Tier 1 (high quality) to Tier 3 (low quality). Specifically, these definitions are as follows:

- Tier 1: A study is rated as "definitely low" or "probably low" ROB for the majority of questions and is not rated as "definitely high" ROB for any question.
- Tier 2: Study meets criteria for neither the first nor third tiers.
- Tier 3: A study is rated as "definitely high" or "probably high" ROB for the majority of questions.

Any study ranked Tier 3 was not evaluated further. All Tier 1 and Tier 2 papers were further considered for feasibility in conducting additional analysis.

For the purposes of this document, the EPA is not selecting a key paper (or papers) on which to rely to inform the derivation of an MCLG for perchlorate (though any study ranked as Tier 3 was not evaluated further). Instead, this report presents evaluations of all identified papers with relevant and necessary data and approaches for how they may inform the derivation of an MCLG.

5.2.4 Step 4. Identify Group 1 Studies That Present Data to Inform a Dose-Response Relationship

After conducting the ROB evaluation, the EPA reviewed all Group 1 studies to identify those for which additional quantitative analysis could be conducted; that is, the studies that were identified as evaluating a continuous measure of fT4 and neurodevelopment and had all the requisite data to perform additional analysis to potentially inform the derivation of an MCLG.

5.3 Results of Evaluation to Identify Studies That Directly Relate Thyroid Hormone Levels with Neurodevelopment

As presented in [REF _Ref456203910 \h], the literature review identified 71 studies that link thyroid hormone levels to neurodevelopmental effects. These studies were divided into three groups to facilitate evaluation:

- Group 1: Studies that may be able to quantitatively describe a relationship between incremental alterations in maternal thyroid hormone levels and alterations in offspring neurodevelopment. (These studies were then further categorized into tiers based on the ROB evaluation.)
- Group 2: Studies that do not have data from which to derive a quantitative relationship between maternal thyroid hormones and offspring neurodevelopment, but instead present only categorical analysis with thyroid hormones below and above a defined cut point and adverse neurodevelopmental outcomes.
- Group 3: Studies that present an analysis that is not directly compatible with BBDR output. For example, if the study evaluated data in pre-term infants or late-term pregnant women it would not inform use of the BBDR output.

Figure [SEQ Figure * ARABIC]. Overview of Process and Results to Assess Studies Relating Thyroid Hormone Levels to Neurodevelopmental Outcomes

[EMBED Visio.Drawing.15]

Following the process outlined above, 16 studies were ultimately identified as Group 1 and subsequently evaluated to determine if relevant and necessary data were available for further analysis. Five of the Group 1 studies conducted analyses or presented data that would allow the EPA to quantitatively connect the results of the BBDR model to incremental changes in adverse neurodevelopmental effects. The following sections provide more detail about the process involved in each step of the evaluation and the results.

5.3.1 Results of Step 1

Out of the 71 papers identified in the literature review, the EPA identified 40 that are not compatible with BBDR model results. These Group 3 studies are listed in [REF _Ref425459365 \h] along with the reason the study is not compatible with BBDR model results. [REF _Ref425459365 \h] also lists the life stage of thyroid hormone measurement to aid in comparison across studies. Summaries of each study in Group 3 are presented in Appendix F.

Table [SEQ Table * ARABIC]. List of Studies Identified in Step 1 and Categorized as Group 3 with Rationale for Categorization

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]

Andersen et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Andersen</Author><Year>2017</Year><RecNum>2023</RecNum><DisplayText>(2017)</DisplayText><record><rec-number>2023</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1533923738">2023</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Andersen, S.L.</author><author>Andersen, S.</author><author>Liew, Z.</author><author>Vestergaard, P.</author><author>Olsen, J.</author></authors></contributors><titles><title>Maternal thyroid function in early pregnancy and neuropsychological performance of the child at 5 years of age</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>660-670</pages><volume>103</volume><number>2</number><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>] *Maternal Thyroid Function in Early Pregnancy and Neuropsychological Performance of the Child at 5 Years of Age*	The study design is not directly relevant to the BBDR model results. This study compared women with thyroid dysfunction to those without dysfunction. While there are data on fT4 concentrations and neurodevelopmental outcomes, these evaluations included women with overt hypothyroidism and therefore cannot be evaluated with respect only to hypothyroxinemia. For several endpoints (i.e., motor function	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
	and behavioral problems) they did note that higher associations related to thyroid dysfunction were likely due to hypothyroxinemia, but no quantitative analysis was provided.	

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Casey et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] *Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy*	The study design is not directly relevant to the BBDR model results. This study examined the impact of treatment of maternal hypothyroxinemia on infant neurodevelopmental outcome, not the relationship between maternal hypothyroxinemia and infant neurodevelopmental outcome.	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Chevrier et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Chevrier</Author><Year>2011</Year><RecNum>5</RecNum><DisplayText>(2011)</DisplayText><record><rec-number>5</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047628">5</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Chevrier, J</author><author>Harley, K G</author><author>Kogut, K</author><author>Holland, N</author><author>Johnson, C</author><author>Eskenazi, B</author></authors></contributors><titles><title>Maternal thyroid function during the second half of pregnancy and child neurodevelopment at 6, 12, 24, and 60 months of age</title><secondary-title>Journal of Thyroid Research</secondary-title></titles><periodical><full-title>Journal of Thyroid Research</full-title></periodical><pages>13</pages><volume>2011</volume><dates><year>2011</year></dates><urls></urls><electronic-resource-num>10.4061/2011/426427</electronic-resource-num></record></Cite></EndNote>] *Maternal Thyroid Function during the Second Half of Pregnancy and Child Neurodevelopment at 6, 12, 24, and 60 Months of Age*	The study population's exposure window (i.e., when the thyroid hormone measurements are taken) does not overlap with the outputs for the BBDR model. This study measured maternal thyroid hormones after 16 GW.	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Craig et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Craig</Author><Year>2012</Year><RecNum>8</RecNum><DisplayText>(2012)</DisplayText><record><rec-number>8</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047630">8</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Craig, W Y</author><author>Allan, W C</author><author>Kloza, E M</author><author>Pulkkinen, A J</author><author>Waisbren, S</author><author>Spratt, D I</author><author>Palomaki, G E</author><author>Neveaux, L M</author><author>Haddow, J E</author></authors></contributors><titles><title>Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>E22-E28</pages><volume>97</volume><number>1</number><section>E22</section><dates><year>2012</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2011-1772</electronic-resource-num></record></Cite></EndNote>] *Mid-Gestational Maternal Free Thyroxine Concentration and Offspring Neurocognitive Development at Age Two Years*	The study population's exposure window does not overlap with the outputs for the BBDR model. This study measured maternal thyroid hormones after 16 GW.	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Cusick and Georgieff [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Cusick</Author><Year>2016</Year><RecNum>306</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>306</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832047">306</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Cusick, S. E.</author><author>Georgieff, M. K.</author></authors></contributors><auth-address>Department of Pediatrics, University of Minnesota School of Medicine, Minneapolis, MN.
Department of Pediatrics, University of Minnesota School of Medicine, Minneapolis, MN. Electronic address: georg001@umn.edu.</auth-address><titles><title>The role of nutrition in brain development: The golden opportunity of the "First 1000 Days"</title><secondary-title>The Journal of Pediatrics</secondary-title></titles><periodical><full-title>The Journal of Pediatrics</full-title></periodical><pages>16-21</pages><volume>175</volume><dates><year>2016</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>1097-6833 (Electronic)
0022-3476 (Linking)</isbn><accession-num>27266965</accession-num><urls><related-urls><url><style face="underline" font="default" size="100%">http://www.ncbi.nlm.nih.gov/pubmed/27266965</style></url></related-urls></urls><custom2>PMC4981537</custom2><electronic-resource-num>10.1016/j.jpeds.2016.05.013</electronic-resource-num></record></Cite></EndNote>] *The Role of Nutrition in Brain Development: The Golden Opportunity of the "First 1000 Days"*	The study design is not directly relevant to the BBDR model results. This is a review paper that provides a narrative discussion and does not provide quantitative information to measure neurodevelopmental outcomes.	N/A - Thyroid measurements were not taken

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Dosiou and Medici [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Dosiou</Author><Year>2017</Year><RecNum>325</RecNum><DisplayText>(2017)</DisplayText><record><rec-number>325</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832531">325</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Dosiou, C.</author><author>Medici, M.</author></authors></contributors><auth-address>Division of EndocrinologyStanford University School of Medicine, Stanford, California, USA cdosiou@stanford.edu m.medici@erasmusmc.nl.
Department of Endocrinology and Rotterdam Thyroid CenterErasmus Medical Center, Rotterdam, The Netherlands cdosiou@stanford.edu m.medici@erasmusmc.nl.</auth-address><titles><title>Management of endocrine disease: Isolated maternal hypothyroxinemia during pregnancy: knowns and unknowns</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>R21-R38</pages><volume>176</volume><number>1</number><keywords><keyword>Animals</keyword><keyword>Disease Management</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Hypothyroidism/*complications/drug therapy</keyword><keyword>Pregnancy</keyword><keyword>Pregnancy Complications</keyword><keyword>Pregnancy Trimester, First</keyword><keyword>Randomized Controlled Trials as Topic</keyword></keywords><dates><year>2017</year><pub-dates><date>Jan</date></pub-dates></dates><isbn>1479-683X (Electronic)
0804-4643 (Linking)</isbn><accession-num>27528503</accession-num><urls><related-urls><url><style face="underline" font="default" size="100%">http://www.ncbi.nlm.nih.gov/pubmed/27528503</style></url></related-urls></urls><electronic-resource-num>10.1530/EJE-16-0354</electronic-resource-num></record></Cite></EndNote>] *Management of Endocrine Disease: Isolated Maternal Hypothyroxinemia during Pregnancy: Knowns and Unknowns*	The study design is not directly relevant to the BBDR model results. This is a review paper that does not provide quantitative information on the relationship between fT4 and outcomes.	Pregnant woman
Fetene et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Fetene</Author><Year>2017</Year><RecNum>1951</RecNum><DisplayText>(2017)</DisplayText><record><rec-number>1951</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1516819484">1951</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fetene, Dagnachew Muluye</author><author>Betts, Kim S</author><author>Alati, Rosa</author></authors></contributors><titles><title>Mechanisms in endocrinology: Maternal thyroid dysfunction during pregnancy and behavioural and psychiatric disorders of children: a systematic review</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>R261-R273</pages><volume>177</volume><number>5</number><dates><year>2017</year></dates><isbn>0804-4643</isbn><urls></urls></record></Cite></EndNote>] *Maternal Thyroid Dysfunction during Pregnancy and Behavioural and Psychiatric Disorders of Children: A Systematic Review*	The study design is not directly relevant to the BBDR model results. This is a review article that does not provide a quantitative meta-analysis.	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Furnica et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] *Update on a New Controversy in Endocrinology: Isolated Maternal Hypothyroxinemia*	The study design is not directly relevant to the BBDR model results. This is a review paper that does not provide quantitative information on the relationship between fT4 and outcomes.	Pregnant woman
Getahun et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Getahun</Author><Year>2017</Year><RecNum>1955</RecNum><DisplayText>(2017)</DisplayText><record><rec-number>1955</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1516819485">1955</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Getahun, Darios</author><author>Jacobsen, Steven J</author><author>Fassett, Michael J</author><author>Wing, Deborah A</author><author>Xiang, Anny H</author><author>Chiu, Vicki</author><author>Peltier, Morgan R</author></authors></contributors><titles><title>Association between maternal hypothyroidism and autism spectrum disorders in the children</title><secondary-title>Pediatric Research</secondary-title></titles><periodical><full-title>Pediatric research</full-title></periodical><dates><year>2017</year></dates><isbn>1530-0447</isbn><urls></urls></record></Cite></EndNote>] *Association between Maternal Hypothyroidism and Autism Spectrum Disorders in the Children*	The study design is not directly relevant to the BBDR model results. This paper evaluated the relationship between maternal hypothyroidism and autism spectrum disorders.	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Ghassabian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2012</Year><RecNum>2206</RecNum><DisplayText>(2012)</DisplayText><record><rec-number>2206</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1542054611">2206</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A.</author><author>Bongers-Schokking, JJ</author><author>de Rijke, YB</author><author>van Mil, N</author><author>Jaddoe, VW</author><author>de Muinck Keizer-Schrama, SM</author><author>Hooijkaas, H</author><author>Hofman, A</author><author>Visser, W</author><author>Roman, GC</author><author>Visser, TJ</author><author>Verhulst, FC</author><author>Tiemeier, H</author></authors></contributors><titles><title>Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: The Generation R Study</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>178-186</pages><volume>22</volume><number>2</number><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>] *Maternal Thyroid Autoimmunity During Pregnancy and the Risk of Attention Deficit/Hyperactivity Problems in Children: The Generation R Study*	The study design is not directly relevant to the BBDR model results. This study examined maternal thyroid antibody status as associated with neurodevelopmental outcomes. Although thyroid hormone levels were assessed, they were not evaluated in the context of their impact on neurodevelopment.	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Gutleb, Cambier, and Serchi [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Gutleb</Author><Year>2016</Year><RecNum>309</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>309</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832134">309</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Gutleb, A.</author><author>Cambier, S.</author><author>Serchi, T.</author></authors></contributors><titles><title>Impact of endocrine distruptors on the thyroid system</title><secondary-title>Hormone Research in Paediatrics</secondary-title></titles><periodical><full-title>Hormone Research in Paediatrics</full-title></periodical><pages>271-278</pages><volume>86</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] *Impact of Endocrine Disruptors on the Thyroid Hormone System*	The study design is not directly relevant to the BBDR model results. This study reviewed the effects that endocrine disruptors may have on the thyroid and did not evaluate the impact of thyroid hormones on neurodevelopment in offspring.	N/A - Thyroid measurements were not taken

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Haddow et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Haddow</Author><Year>1999</Year><RecNum>37</RecNum><DisplayText>(1999)</DisplayText><record><rec-number>37</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062207">37</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Haddow, J E</author><author>Palomaki, G E</author><author>Allan, W C</author><author>Williams, J R</author><author>Knight, G J</author><author>Gagnon, J</author><author>O'Heir, C E</author><author>Mitchell, M L</author><author>Hermos, R J</author><author>Waisbren, S E</author><author>Faix, J D</author><author>Klein, R Z</author></authors></contributors><titles><title>Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child</title><secondary-title>The New England Journal of Medicine</secondary-title></titles><periodical><full-title>The New England Journal of Medicine</full-title></periodical><pages>549-559</pages><volume>341</volume><number>8</number><section>549</section><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>] *Maternal Thyroid Deficiency During Pregnancy and Subsequent Neuropsychological Development of the Child*	The study design is not directly relevant to the BBDR model results. The study concentrated on the impact of maternal hypothyroidism and offspring neurodevelopment. Data were not presented to allow for an understanding of the relationship between incremental changes in thyroid hormones, or maternal hypothyroxinemia, and neurodevelopmental changes.	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Hamza, Hewedi, and Sallam [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Hamza</Author><Year>2013</Year><RecNum>14</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047634">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hamza, R T</author><author>Hewedi, D H</author><author>Sallam, M T</author></authors></contributors><titles><title>Iodine deficiency in Egyptian autistic children and their mothers: relation to disease severity</title><secondary-title>Archives of Medical Research</secondary-title></titles><periodical><full-title>Archives of Medical Research</full-title></periodical><pages>555-561</pages><volume>44</volume><section>555</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1016/j.arcmed.2013.09.012</electronic-resource-num></record></Cite></EndNote>] *Iodine Deficiency in Egyptian Autistic Children and Their Mothers: Relation to Disease Severity*	The study population's exposure window does not overlap with the outputs for the BBDR model. The study measured thyroid hormones in autistic children.	Child
Hollanders et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] *No Association Between Transient Hypothyroxinemia of Prematurity and Neurodevelopmental Outcome in Young Adulthood*	The study design is not directly relevant to the BBDR model results. The study assesses the impact of transient hypothyroxinemia of prematurity in pre-term or very low birthweight infants.	Neonate, child

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Hollanders et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Hollanders</Author><Year>2016</Year><RecNum>312</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>312</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832203">312</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hollanders, J. J.</author><author>van der Pal, S. M.</author><author>Verkerk, P. H.</author><author>Rotteveel, J.</author><author>Finken, M. J.</author><author>Dutch, Pops-Collaborative Study Group</author></authors></contributors><auth-address>Department of Pediatrics, VU University Medical Center, 1007 MB Amsterdam, The Netherlands. Electronic address: j.hollanders@vumc.nl.
TNO, Child Health, 2316 ZL Leiden, The Netherlands.
Department of Pediatrics, VU University Medical Center, 1007 MB Amsterdam, The Netherlands.</auth-address><titles><title>Transient hypothyroxinemia of prematurity and problem behavior in young adulthood</title><secondary-title>Psychoneuroendocrinology</secondary-title></titles><periodical><full-title>Psychoneuroendocrinology</full-title></periodical><pages>40-6</pages><volume>72</volume><keywords><keyword>Adolescence</keyword><keyword>Behavior</keyword><keyword>Behavioral problems</keyword><keyword>Hypothyroxinemia</keyword><keyword>Hypothyroxinemia of prematurity</keyword><keyword>Prematurity</keyword><keyword>Problem behavior</keyword><keyword>Young adults</keyword></keywords><dates><year>2016</year><pub-dates><date>Oct</date></pub-dates></dates><isbn>1873-3360 (Electronic)
0306-4530 (Linking)</isbn><accession-num>27343725</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/27343725</url></related-urls></urls><electronic-resource-num>10.1016/j.psyneuen.2016.06.008</electronic-resource-num></record></Cite></EndNote>] *Transient Hypothyroxinemia of Prematurity and Problem Behavior in Young Adulthood*	The study design is not directly relevant to the BBDR model results. The study assessed the impact of transient hypothyroxinemia of prematurity in pre-term infants or very low birthweight infants.	Neonate, child

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Hoshiko, Grether, Windham, Smith, and Fessel [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Hoshiko</Author><Year>2011</Year><RecNum>17</RecNum><DisplayText>(2011)</DisplayText><record><rec-number>17</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047636">17</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hoshiko, S</author><author>Grether, J K</author><author>Windham, G C</author><author>Smith, D</author><author>Fessel, K</author></authors></contributors><titles><title>Are thyroid hormone concentrations at birth associated with subsequent autism diagnosis?</title><secondary-title>Autism Research</secondary-title></titles><periodical><full-title>Autism research</full-title></periodical><pages>456-463</pages><volume>4</volume><section>456</section><dates><year>2011</year></dates><urls></urls><electronic-resource-num>10.1002/aur.219</electronic-resource-num></record></Cite></EndNote>] *Are Thyroid Hormone Concentrations at Birth Associated with Subsequent Autism Diagnosis?*	The study population's exposure window does not overlap with the outputs for the BBDR model. Thyroid hormone samples were measured in neonates within 24 hours of birth.	Neonate
Korzeniewski et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Korzeniewski</Author><Year>2013</Year><RecNum>20</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>20</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047638">20</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korzeniewski, S J</author><author>Pinto-Martin, J A</author><author>Whitaker, A H</author><author>Feldman, J F</author><author>Lorenz, J M</author><author>Levy, S E</author><author>Movsas, T Z</author><author>Pappas, A</author><author>Paneth, N</author></authors></contributors><titles><title>Association between transient hypothyroxinemia of prematurity and adult autism spectrum disorder in a low-birthweight cohort: an exploratory study</title><secondary-title>Pediatric and Perinatal Epidemiology</secondary-title></titles><periodical><full-title>Pediatric and Perinatal Epidemiology</full-title></periodical><pages>182-187</pages><volume>27</volume><section>182</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1111/ppe.12034</electronic-resource-num></record></Cite></EndNote>] *Association Between Transient Hypothyroxinemia of Prematurity and Adult Autism Spectrum Disorder in a Low-Birthweight Cohort: An Exploratory Study*	The study design is not directly relevant to the BBDR model results. The study only examined low-birthweight/pre-term infants.	Neonate

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Lazarus et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lazarus</Author><Year>2012</Year><RecNum>2025</RecNum><DisplayText>(2012)</DisplayText><record><rec-number>2025</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1533926600">2025</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lazarus, J., </author><author>Bestwick, J. P., </author><author>Channon, S., </author><author>Paradice, R., </author><author>Maina, A., </author></authors></contributors><titles><title>Antenatal thyroid screening and childhood cognitive function</title><secondary-title>New England Journal of Medicine</secondary-title></titles><periodical><full-title>New England Journal of Medicine</full-title></periodical><volume>366</volume><number>6</number><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>] *Antenatal Thyroid Screening and Childhood Cognitive Function*	The study design is not directly relevant to the BBDR model results. This study examined the impact of treatment of maternal hypothyroxinemia on infant neurodevelopmental outcome, not the relationship between maternal hypothyroxinemia and infant neurodevelopmental outcome.	Pregnant woman, infant

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Leung [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Leung</Author><Year>2015</Year><RecNum>315</RecNum><DisplayText>(2015)</DisplayText><record><rec-number>315</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832294">315</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Leung, A. M.</author></authors></contributors><titles><title>Maternal hypothyroxinemia in the late first trimester may affect offspring math performance at 5 years of age</title><secondary-title>Clinical Thyroidology</secondary-title></titles><periodical><full-title>Clinical Thyroidology</full-title></periodical><pages>266-268</pages><volume>27</volume><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>] *Maternal Hypothyroxinemia in the Late First Trimester May Affect Offspring Math Performance At 5 Years of Age*	The study design is not directly relevant to the BBDR model results. This is a narrative discussion of Noten et al. (2015).	Pregnant woman
Lyall et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Lyall</Author><Year>2016</Year><RecNum>316</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>316</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832313">316</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lyall, K.</author><author>Anderson, M.</author><author>Kharrazi, M.</author><author>Windham, G. C.</author></authors></contributors><auth-address>California Department of Public Health, Environmental Health Investigations Branch, 850 Marina Bay Parkway, Richmond, California, 94804. kld98@drexel.edu.
Impact Assessment, Inc, La Jolla, California.
California Department of Public Health, Environmental Health Investigations Branch, 850 Marina Bay Parkway, Richmond, California, 94804.</auth-address><titles><title>Neonatal thyroid hormone levels in association with autism spectrum disorder</title><secondary-title>Autism Research </secondary-title></titles><periodical><full-title>Autism research</full-title></periodical><keywords><keyword>autism spectrum disorder</keyword><keyword>neonatal hormones</keyword><keyword>risk factors</keyword><keyword>thyroid hormones</keyword></keywords><dates><year>2016</year><pub-dates><date>Oct 14</date></pub-dates></dates><isbn>1939-3806 (Electronic)
1939-3806 (Linking)</isbn><accession-num>27739255</accession-num><urls><related-urls><url><style face="underline" font="default" size="100%">http://www.ncbi.nlm.nih.gov/pubmed/27739255</style></url></related-urls></urls><electronic-resource-num>10.1002/aur.1708</electronic-resource-num></record></Cite></EndNote>] *Neonatal Thyroid Hormone Levels in Association with Autism Spectrum Disorder*	The study population's exposure window does not overlap with the outputs for the BBDR model. The study only measured thyroid hormones (T4 and TSH) in bloodspots of newborn infants.	Neonate

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Man, Brown, and Serunian [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Man</Author><Year>1991</Year><RecNum>38</RecNum><DisplayText>(1991)</DisplayText><record><rec-number>38</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062207">38</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Man, E B</author><author>Brown, J F</author><author>Serunian, S A</author></authors></contributors><titles><title>Maternal hypothyroxinemia: Psychoneurological deficits of progeny</title><secondary-title>Annals of Clinical and Laboratory Science</secondary-title></titles><periodical><full-title>Annals of Clinical and Laboratory Science</full-title></periodical><pages>227-239</pages><volume>21</volume><number>4</number><section>227</section><dates><year>1991</year></dates><urls></urls><electronic-resource-num>0091-7370/91/0700-0227</electronic-resource-num></record></Cite></EndNote>] *Maternal Hypothyroxinemia: Psychoneurological Deficits of Progeny*	The study design is not directly relevant to the BBDR model results. The study measured butanol-extractable iodine and did not include data on T4 or fT4.	Pregnant woman
Min et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] *Maternal Hypothyroxinemia-Induced Neurodevelopmental Impairments in the Progeny*	The study design is not directly relevant to the BBDR model results. This is a review paper that does not provide quantitative information to measure neurodevelopmental outcomes.	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Moog et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Moog</Author><Year>2017</Year><RecNum>1952</RecNum><DisplayText>(2017)</DisplayText><record><rec-number>1952</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1516819484">1952</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Moog, Nora K</author><author>Entringer, Sonja</author><author>Heim, Christine</author><author>Wadhwa, Pathik D</author><author>Kathmann, Norbert</author><author>Buss, Claudia</author></authors></contributors><titles><title>Influence of maternal thyroid hormones during gestation on fetal brain development</title><secondary-title>Neuroscience</secondary-title></titles><periodical><full-title>Neuroscience</full-title><abbr-1>Neuroscience</abbr-1></periodical><pages>68-100</pages><volume>342</volume><dates><year>2017</year></dates><isbn>0306-4522</isbn><urls></urls></record></Cite></EndNote>] *Influence of Maternal Thyroid Hormones During Gestation on Fetal Brain Development*	The study design is not directly relevant to the BBDR model results. This is a review article that does not provide a quantitative meta-analysis.	Pregnant woman
Muñoz, Figueras, & Puig [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Muñoz</Author><Year>2009</Year><RecNum>2207</RecNum><DisplayText>(2009)</DisplayText><record><rec-number>2207</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1542054961">2207</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Muñoz, M.</author><author>Figueras, F. </author><author>Puig, M</author></authors></contributors><titles><title>La hipotiroxinemia gestacional se asocia al síndrome de déficit de atención e hiperactividad</title><secondary-title>Progresos de Obstetricia y Ginecología</secondary-title></titles><periodical><full-title>Progresos de Obstetricia y Ginecología</full-title></periodical><pages>681-685</pages><volume>52</volume><number>12</number><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>] *Low Maternal Free Thyroxine Concentrations during Pregnancy Is Associated with Attention-Deficit/Hyperactivity Disorder* [Spanish]	The study population's exposure window does not overlap with the output of the BBDR model. This study measures thyroid hormones in the third trimester.[b]	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Pearce [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pearce</Author><Year>2015</Year><RecNum>324</RecNum><DisplayText>(2015a)</DisplayText><record><rec-number>324</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832512">324</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pearce, E.N.</author></authors></contributors><titles><title>Maternal hypothyroxinemia in pregnancy is associated with increased risk for ADHD symptoms in children</title><secondary-title>Clinical Thyroidology</secondary-title></titles><periodical><full-title>Clinical Thyroidology</full-title></periodical><pages>212-214</pages><volume>27</volume><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>] *Maternal Hypothyroxinemia in Pregnancy Is Associated with Increased Risk for ADHD Symptoms in Children*	The study design is not directly relevant to the BBDR model results. This is a narrative discussion of Modesto et al. (2015).	Pregnant woman
Pérez-Lobato et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pérez-Lobato</Author><Year>2014</Year><RecNum>24</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>24</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">24</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pérez-Lobato, R</author><author>Ramos, R</author><author>Arrebola, J P</author><author>Calvente, I</author><author>Ocón-Hernández, O</author><author>Dávila-Arias, C</author><author>Pérez-García, M</author><author>Olea, N</author><author>Fernández, M F</author></authors></contributors><titles><title>Thyroid status and its association with cognitive functioning in healthy boys at 10 years of age</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>129-139</pages><volume>172</volume><number>2</number><section>129</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1530/EJE-14-0093</electronic-resource-num></record></Cite></EndNote>] *Thyroid Status and Its Association with Cognitive Functioning in Healthy Boys at 10 Years of Age*	The study population's exposure window does not overlap with the outputs for the BBDR model. Thyroid hormones were measured in children (mean age was 9.8 years).	Child

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Pharoah, Connolly, Ekins, and Harding [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pharoah</Author><Year>1984</Year><RecNum>39</RecNum><DisplayText>(1984)</DisplayText><record><rec-number>39</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062207">39</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pharoah, P O D</author><author>Connolly, K J</author><author>Ekins, R P</author><author>Harding, A G</author></authors></contributors><titles><title>Maternal thyroid hormone levels in pregnancy and the subsequent cognitive and motor performance of the children</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>265-270</pages><volume>21</volume><section>265</section><dates><year>1984</year></dates><urls></urls></record></Cite></EndNote>] *Maternal Thyroid Hormone Levels in Pregnancy and the Subsequent Cognitive and Motor Performance of the Children*	The study design is not directly relevant to the BBDR model results. The study population was severely iodine-deficient.	Pregnant woman
Scratch et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Scratch</Author><Year>2014</Year><RecNum>27</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>27</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047642">27</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Scratch, S E</author><author>Hunt, R W</author><author>Thompson, D K</author><author>Ahmadzai, Z M</author><author>Doyle, L W</author><author>Inder, T E</author><author>Anderson, P J</author></authors></contributors><titles><title>Free thyroxine levels after very preterm birth and neurodevelopmental outcomes at age 7 years</title><secondary-title>Pediatrics</secondary-title></titles><periodical><full-title>Pediatrics</full-title></periodical><pages>e955-e963</pages><volume>133</volume><number>4</number><section>e955</section><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>] *Free Thyroxine Levels After Very Preterm Birth and Neurodevelopmental Outcomes at Age 7 Years*	The study design is not directly relevant to the BBDR model results. The study only examined very pre-term births.	Neonate

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Soldin et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Soldin</Author><Year>2002</Year><RecNum>28</RecNum><DisplayText>(2002)</DisplayText><record><rec-number>28</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047642">28</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Soldin, O.P.</author><author>Nandedkar, A.K.N.</author><author>Japal, K.M.</author><author>Stein, M</author><author>Mosee, S</author><author>Magrab, P</author><author>Lai, S</author><author>Lamm, S.H.</author></authors></contributors><titles><title>Newborn thyroxine levels and childhood ADHD</title><secondary-title>Clinical Biochemistry</secondary-title></titles><periodical><full-title>Clinical Biochemistry</full-title></periodical><pages>131-145</pages><volume>35</volume><number>2</number><section>131</section><dates><year>2002</year></dates><urls></urls></record></Cite></EndNote>] *Newborn Thyroxine Levels and Childhood ADHD*	The study population's exposure window does not overlap with outputs for the BBDR model. The study only measured thyroid hormones in infants.	Neonate
Soldin, Lai, Lamm, and Mosee [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Soldin</Author><Year>2003</Year><RecNum>29</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>29</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047643">29</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Soldin, O.P.</author><author>Lai, S</author><author>Lamm, S H</author><author>Mosee, S</author></authors></contributors><titles><title>Lack of a relation between human neonatal thyroxine and pediatric neurobehavioral disorders</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>193-204</pages><volume>13</volume><number>2</number><section>193</section><dates><year>2003</year></dates><urls></urls><electronic-resource-num>10.1089/105072503321319503</electronic-resource-num></record></Cite></EndNote>] *Lack of a Relation Between Human Neonatal Thyroxine and Pediatric Neurobehavioral Disorders*	The study population's exposure window does not overlap with outputs for the BBDR model. The study only measured thyroid hormones in infants.	Neonate

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Suárez-Rodríguez, Azcona-San Julián, and Alzina de Aguilar [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Suarez-Rodriguez</Author><Year>2012</Year><RecNum>1888</RecNum><DisplayText>(2012)</DisplayText><record><rec-number>1888</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1497462591">1888</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Suárez-Rodriguez, Marta</author><author>Azcona-San Julián, Cristina</author><author>Alzina de Aguilar, Valentin</author></authors></contributors><titles><title>Hypothyroxinemia during pregnancy: the effect on neurodevelopment in the child</title><secondary-title>International Journal of Developmental Neuroscience</secondary-title></titles><periodical><full-title>International Journal of Developmental Neuroscience</full-title></periodical><pages>435-438</pages><volume>30</volume><number>6</number><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>] *Hypothyroxinemia during Pregnancy: The Effect on Neurodevelopment in the Child*	The study population's exposure window does not overlap with the outputs for the BBDR model. This study measured maternal thyroid hormones after 16 GW.	Pregnant woman
Tiemeier and Korevaar [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Tiemeier</Author><Year>2016</Year><RecNum>326</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>326</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832556">326</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Tiemeier, H.</author><author>Korevaar, T. I.</author></authors></contributors><auth-address>Department of Child and Adolescent Psychiatry, Erasmus Medical Center, Rotterdam, The Netherlands; Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands.
Department of Internal Medicine Erasmus Medical Center, Rotterdam, The Netherlands; Department of Rotterdam Thyroid Center, Erasmus Medical Center, Rotterdam, The Netherlands. Electronic address: h.tiemeier@erasmusmc.nl.</auth-address><titles><title>A new modifiable risk factor for schizophrenia?</title><secondary-title>Biological Psychiatry</secondary-title></titles><periodical><full-title>Biological Psychiatry</full-title></periodical><pages>950-1</pages><volume>79</volume><number>12</number><dates><year>2016</year><pub-dates><date>Jun 15</date></pub-dates></dates><isbn>1873-2402 (Electronic)
0006-3223 (Linking)</isbn><accession-num>27241000</accession-num><urls><related-urls><url><style face="underline" font="default" size="100%">http://www.ncbi.nlm.nih.gov/pubmed/27241000</style></url></related-urls></urls><electronic-resource-num>10.1016/j.biopsych.2016.04.004</electronic-resource-num></record></Cite></EndNote>] *A New Modifiable Risk Factor for Schizophrenia?*	The study design is not directly relevant to the BBDR model results. This is a commentary article that does not provide quantitative information to measure neurodevelopmental outcomes.	N/A - Thyroid measurements were not taken

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Velasco et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Velasco</Author><Year>2009</Year><RecNum>41</RecNum><DisplayText>(2009)</DisplayText><record><rec-number>41</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062208">41</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Velasco, I</author><author>Carreira, M</author><author>Santiago, P</author><author>Muela, J A</author><author>García-Fuentes, E</author><author>Sánchez-Muñoz, B</author><author>Garriga, M J</author><author>González-Fernández, M C</author><author>Rodríguez, A</author><author>Caballero, F F</author><author>Machado, A</author><author>González-Romero, S</author><author>Anarte, M T</author><author>Soriguer, F</author></authors></contributors><titles><title>Effect of iodine prophylaxis during pregnancy on neurocognitive development of children during the first two years of life</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>3234-3231</pages><volume>94</volume><number>9</number><section>3234</section><dates><year>2009</year></dates><isbn>0021-972X
1945-7197</isbn><urls></urls><electronic-resource-num>10.1210/jc.2008-2652</electronic-resource-num></record></Cite></EndNote>] *Effect of Iodine Prophylaxis during Pregnancy on Neurocognitive Development of Children during the First Two Years of Life*	The study population's exposure window does not overlap with the outputs for the BBDR model. This study measured maternal thyroid hormones after 16 GW.	Pregnant woman
Vermiglio et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Vermiglio</Author><Year>2004</Year><RecNum>33</RecNum><DisplayText>(2004)</DisplayText><record><rec-number>33</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047646">33</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Vermiglio, F</author><author>Lo Presti, V P</author><author>Moleti, M</author><author>Sidoti, M</author><author>Tortorella, G</author><author>Scaffidi, G</author><author>Castagna, M G</author><author>Mattina, F</author><author>Violi, M A</author><author>Crisà, A</author><author>Artemisia, A</author><author>Trimarchi, F</author></authors></contributors><titles><title>Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>6054-6060</pages><volume>89</volume><number>12</number><section>6054</section><dates><year>2004</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2004-0571</electronic-resource-num></record></Cite></EndNote>] *Attention Deficit and Hyperactivity Disorders in the Offspring of Mothers Exposed to Mild-Moderate Iodine Deficiency: A Possible Novel Iodine Deficiency Disorder in Developed Countries*	The study population's exposure window does not overlap with the outputs for the BBDR model. This study measured maternal thyroid hormones after 16 GW.	Pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
F. Williams et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Williams</Author><Year>2012</Year><RecNum>34</RecNum><DisplayText>(2012)</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047646">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, F</author><author>Watson, J</author><author>Ogston, S</author><author>Hume, R</author><author>Willatts, P</author><author>Visser, T</author><author>Scottish Preterm Thyroid Group,</author></authors></contributors><titles><title>Mild maternal thyroid dysfunction at delivery of infants born ≤34 weeks and neurodevelopmental outcome at 5.5 years</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1977-1985</pages><volume>97</volume><number>6</number><section>1977</section><dates><year>2012</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2011-2451</electronic-resource-num></record></Cite></EndNote>] *Mild Maternal Thyroid Dysfunction at Delivery of Infants Born ≤34 Weeks and Neurodevelopmental Outcome at 5.5 Years*	The study design is not directly relevant to the BBDR model results. This study evaluated the effect of maternal thyroid dysfunction on pre-term infants.	Neonate, pregnant woman
F. Williams et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Williams</Author><Year>2013</Year><RecNum>35</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047647">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Williams, F</author><author>Watson, J</author><author>Ogston, S A</author><author>Visser, T J</author><author>Hume, R</author><author>Willatts, P</author></authors></contributors><titles><title>Maternal and umbilical cord levels of T4, FT4, TSH, TPOAb, and TgAb in term infants and neurodevelopmental outcome at 5.5 years</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>829-838</pages><volume>98</volume><number>2</number><section>829</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3572</electronic-resource-num></record></Cite></EndNote>] *Maternal and Umbilical Cord Levels of T_4, fT4, TSH, TPOAb, and TgAb in Terms Infants and Neurodevelopmental Outcome at 5.5 Years*	The study population's exposure window does not overlap with the outputs for the BBDR model. Maternal fT4 was not evaluated in association with the neurodevelopmental outcome.	Fetus, pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
F. L. R. Williams et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] *Supplemental Iodide for Preterm Infants and Developmental Outcomes at 2 Years: An RCT*	The study population's exposure window does not overlap with the output of the BBDR model. The study evaluated the impact of iodine supplementation in pre-term infants on subsequent neurodevelopment.	Infant
Willoughby [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Willoughby</Author><Year>2011</Year><RecNum>42</RecNum><DisplayText>(2011)</DisplayText><record><rec-number>42</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062209">42</key></foreign-keys><ref-type name="Thesis">32</ref-type><contributors><authors><author>Willoughby, K</author></authors></contributors><titles><title>Effects of early thyroid hormone deficiency on autobiographical memory and hippocampal structure and function during late childhood and early adolescence</title><secondary-title>Graduate Department of Psychology</secondary-title></titles><pages>228</pages><volume>Doctorate of Philosophy</volume><dates><year>2011</year></dates><publisher>University of Toronto</publisher><urls></urls></record></Cite></EndNote>] *Effects of Early Thyroid Hormone Deficiency on Autobiographical Memory and Hippocampal Structure During Late Childhood and Early Adolescence*	The study design is not directly relevant to the BBDR model results. The only results for T4 are related to cases of congenital hypothyroidism.	Child, neonate, pregnant woman

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]
Willoughby, McAndrews, and Rovet [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Willoughby</Author><Year>2014</Year><RecNum>36</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>36</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047648">36</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Willoughby, K</author><author>McAndrews, M P</author><author>Rovet, J F</author></authors></contributors><titles><title>Effects of maternal hypothyroidism on offspring hippocampus and memory</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>576-584</pages><volume>24</volume><number>3</number><section>576</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1089/thy.2013.0215</electronic-resource-num></record></Cite></EndNote>] *Effects of Maternal Hypothyroidism on Offspring Hippocampus and Memory*	The study design is not directly relevant to the BBDR model results. The results of the study pertain to the offspring of hypothyroid women.	Pregnant woman
Wong et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Wong</Author><Year>2016</Year><RecNum>330</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>330</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491838588">330</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Wong, Hilary S.</author><author>Santhakumaran, Shalini</author><author>Cowan, Frances M.</author><author>Modi, Neena</author><author>Medicines for Neonates Investigator Group,</author></authors></contributors><titles><title>Developmental assessments in preterm children: A meta-analysis</title><secondary-title>Pediatrics</secondary-title><short-title>Developmental Assessments in Preterm Children</short-title></titles><periodical><full-title>Pediatrics</full-title></periodical><pages>e20160251</pages><volume>138</volume><number>2</number><dates><year>2016</year><pub-dates><date>2016/08/01/</date></pub-dates></dates><isbn>0031-4005, 1098-4275</isbn><urls><related-urls><url><style face="underline" font="default" size="100%">http://pediatrics.aappublications.org/content/138/2/e20160251</style></url><url><style face="underline" font="default" size="100%">http://www.ncbi.nlm.nih.gov/pubmed/27471220</style></url><url>files/820/e20160251.html</url><url><style face="underline" font="default" size="100%">http://pediatrics.aappublications.org/content/138/2/e20160251.long?sso=1&sso_redirect_count=1&nfstatus=401&nftoken=00000000-0000-0000-0000-000000000000&nfstatusdescription=ERROR%3a+No+local+token</style></url></related-urls></urls><electronic-resource-num>10.1542/peds.2016-0251</electronic-resource-num><remote-database-provider>pediatrics.aappublications.org</remote-database-provider><language>en</language><access-date>2017/01/19/16:47:47</access-date></record></Cite></EndNote>] *Developmental Assessments in Preterm Children: A Meta-Analysis*	The study design is not directly relevant to the BBDR model results. This study evaluated the risk of pre-term birth from thyroid disease.	N/A - Thyroid measurements were not taken

Study	Rationale	Life Stage of Thyroid Hormone Measurement[a]

[a] Pregnant woman: thyroid hormone measurement taken anytime during pregnancy; Fetus: thyroid hormone levels were measured from cord blood at birth. Neonate: thyroid hormone levels were measured from a source other than cord blood between birth and 28 days of age. Child: thyroid hormone levels were measured after 1 year of age.
[b] Assessment based upon presented results from Thompson et al. (2018). The original study is written in Spanish, and the full text was not reviewed at the time of report publication.

5.3.2 Results of Step 2

After identifying 40 studies to categorize as Group 3 in Step 1, 31 studies remained for categorization in Step 2. It was determined whether or not each study presented an analysis that was based on a continuous measure of thyroid hormones. Fifteen studies were placed into Group 2 given that they only presented categorical analyses, and 16 were placed into Group 1 because they presented a continuous regression analysis. Group 1 studies may also have categorical results, but they were categorized based on the presence of any analysis based on a continuous measure of thyroid hormone levels. Summaries of the studies in each group are presented in subsequent sections.

Summary of Group 2 Studies

Of the 31 studies evaluated in Step 2, 15 studies provide categorical data that assist in understanding the implications of altered maternal thyroid hormone levels and potential adverse neurodevelopmental outcomes in their offspring. However, these studies do not present data to inform an analysis that allows for an understanding of the impact of incremental changes in thyroid hormones and subsequent neurodevelopmental impacts. Study results related to cognitive outcomes are summarized in [REF _Ref424646544 \h], behavioral outcomes (including ADHD) are including in [REF _Ref517280585 \h], and studies related to autism are summarized in [REF _Ref517280594 \h] (studies may be repeated between or within tables if they considered a variety of endpoints).

Table [SEQ Table * ARABIC]. Overview of Studies Categorized as Group 2 – Cognition

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Intelligence Quotient					

Grau et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Grau</Author><Year>2015</Year><RecNum>13</RecNum><DisplayText>(2015)</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047634">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Grau, G</author><author>Aguayo, A</author><author>Vela, A</author><author>Aniel-Quiroga, A</author><author>Espada, M</author><author>Miranda, G</author><author>Martinez-Indart, L</author><author>Martul, P</author><author>Castaño, L</author><author>Rica, I</author></authors></contributors><titles><title>Normal intellectual development in children born from women with hypothyroxinemia during their pregnancy</title><secondary-title>Journal of Trace Elements in Medicine and Biology</secondary-title></titles><periodical><full-title>Journal of Trace Elements in Medicine and Biology</full-title></periodical><pages>18-24</pages><volume>31</volume><section>18</section><dates><year>2015</year></dates><urls></urls><electronic-resource-num>10.1016/j.jtemb.2015.02.004</electronic-resource-num></record></Cite></EndNote>] *Normal Intellectual Development in Children Born from Women with Hypothyroxinemia During Their Pregnancy*	455 Spanish mother-child pairs at age 1 assessment 289 Spanish mother-child pairs at age 6-8 assessment (1 yr 1st trimester cases = 47; 1 yr 2nd trimester cases = 42; 6-8 yr 1st trimester cases = 33; 6-8 yr 2nd trimester cases = 28)	fT4 < 10th percentile (< 13.7) (first trimester) fT4 < 10th percentile (11.5 pmol/L) (second trimester)	Child Intelligence *Wechsler Intelligence Scale for Children (WISC) IV*	Children of mothers with hypothyroxinemia in the first and second trimester from an iodine-sufficient area did not have adverse neurodevelopmental outcomes (assessed at age 6 to 8 with the WISC) associated with levels of fT4.	Pregnant woman
Hales et al. (2018)	331 mother-	fT4 < 2.5th percentile[c]	Child IQ	There was no	Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Controlled Antenatal Thyroid Screening II: Effect of Treating Maternal Sub-Optimal Thyroid Function on Child Cognition	child pairs from the UK (n_{cases} = 81; 40 of which were treated with thyroxine)		*Wechsler Intelligence Scale for Children IV*	difference between mean IQ scores of the children born to hypothyroxinemic mothers and those born to mothers with normal gestational thyroid function (*p* = 0.875).	

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Päkkilä et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pakkila</Author><Year>2015</Year><RecNum>323</RecNum><DisplayText>(2015)</DisplayText><record><rec-number>323</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832494">323</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Päkkilä, F</author><author>Männistö, T</author><author>Hartikainen, A-L</author><author>Ruokonen, A.</author><author>et al.,</author></authors></contributors><titles><title>Maternal and child's thyroid function and child's intellect and scholastic performance</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>1363-1374</pages><volume>25</volume><number>12</number><dates><year>2015</year></dates><urls></urls><electronic-resource-num>10.1787/9789264091450-e</electronic-resource-num></record></Cite></EndNote>] *Maternal and Child's Thyroid Function and Child's Intellect and Scholastic Performance*	5,295 Finnish mother-child pairs with sufficient maternal serum samples (n_{cases} = 67)	fT4 < 11.4 in the first trimester fT4 < 11.1 in the second trimester[d]	Child IQ categorized as having mild cognitive limitation if IQ was between 50 and 85 points or severe intellectual deficiency if IQ was less than 50 points *Wechsler Intelligence Scale for Children-Revised*	Maternal thyroid dysfunction was not associated with the prevalence and odds of the child's severe intellectual deficiency or mild cognitive limitation.	Pregnant woman, child

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Bayley Scales (Mental Development Index (MDI) & Psychomotor Development Index (PDI))					

Costeira et al. (2011) *Psychomotor Development of Children from an Iodine-Deficient Region*	86 Portuguese mother-child pairs from iodine-deficient region (n_{cases} = 8)	fT4 < 10th percentile (< 9.0 pg/mL or < 11.6)	Mental Development Index Psychomotor Development Index *Bayley Scales of Infant Development*	Children born to mothers with low fT4 had increased odds of mild-to-severe delay in psychomotor development compared to children born to mothers with fT4 within the population reference range. Neonatal thyroid status did not influence development.	Neonate, pregnant woman
Júlvez et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Julvez</Author><Year>2013</Year><RecNum>18</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>18</rec-number><foreign-keys><key app="EN" db-	1,643 Spanish mother-	Low fT4 (less than 10th (8.89), 5th (8.39)	Mental Development Index	Children born to mothers with lower fT4 (<10th	Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047637">18</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Júlvez, J</author><author>Álvarez-Pedrerol, M</author><author>Rebagliato, M</author><author>Murcia, M</author><author>Forns, J</author><author>Garcia-Esteban, R</author><author>Lertxundi, N</author><author>Espada, M</author><author>Tardón, A</author><author>Galán, I R</author><author>Sunyer, J</author></authors></contributors><titles><title>Thyroxine levels during pregnancy in healthy women and early child neurodevelopment</title><secondary-title>Epidemiology</secondary-title></titles><periodical><full-title>Epidemiology</full-title></periodical><pages>150-157</pages><volume>24</volume><number>1</number><section>150</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1097/EDE.0b013e318276ccd3</electronic-resource-num></record></Cite></EndNote>] *Thyroxine Levels During Pregnancy in Healthy Women and Early Child Neurodevelopment*	child pairs (n_{cases} = 164)	or 2.5th (8.10) percentile)	Psychomotor Development Index *Bayley Scales of Infant Development*	percentile (<8.89 pmol/L)) show a decrease in Bayley score compared to children born to mothers with fT4 > 10th percentile.	

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Li et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Li</Author><Year>2010</Year><RecNum>21</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>21</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047639">21</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Li, Y</author><author>Shan, Z</author><author>Teng, W</author><author>Yu, X</author><author>Li, Y</author><author>Fan, C</author><author>Teng, X</author><author>Guo, R</author><author>Wang, H</author><author>Li, J</author><author>Chen, Y</author><author>Wang, W</author><author>Chawinga, M</author><author>Zhang, L</author><author>Yang, L</author><author>Zhao, Y</author><author>Hua, T</author></authors></contributors><titles><title>Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>825-829</pages><volume>72</volume><section>825</section><dates><year>2010</year></dates><urls></urls><electronic-resource-num>10.1111/j.1365-2265.2009.03743.x</electronic-resource-num></record></Cite></EndNote>] *Abnormalities of Maternal Thyroid Function During Pregnancy Affect Neuropsychological Development of Their Children at 25-30 Months*	57 Chinese mother-child pairs (n_{cases} = 19)	fT4 < 5th percentile (< 11.9)	Mental Development Index Psychomotor Development Index *Bayley Scales of Infant Development*	Children of hypothyroxinemic women had significantly lower mean mental and psychomotor development (Bayley) scores at 25-30 months compared to children of non-hypothyroxinemic women.	Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Other Cognitive Tests					
Berbel et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Berbel</Author><Year>2009</Year><RecNum>4</RecNum><DisplayText>(2009)</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047627">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Berbel, P</author><author>Mestre, J L</author><author>Santamaría, A</author><author>Palazón, I</author><author>Franco, A</author><author>Graells, M</author><author>González-Torga, A</author><author>Morreale de Escobar, G</author></authors></contributors><titles><title>Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>511-519</pages><volume>19</volume><number>5</number><section>511</section><dates><year>2009</year></dates><urls></urls><electronic-resource-num>10.1089/thy2008.0341</electronic-resource-num></record></Cite></EndNote>] *Delayed Neurobehavioral Development in Children Born to Pregnant Women with Mild Hypothyroxinemia During the First Month of Gestation: The Importance of Early Iodine Supplementation*	43 Spanish mother-child pairs in 3 groups based on fT4 level and timing of iodine supplementation[f]	fT4 < 10th percentile (< 10.6)	Neurobehavioral performance (includes gross and fine motor coordination, language skills, and socialization) *Brunet-Lézine scale*	A delay of 6–10 weeks in iodine supplementation of hypothyroxinemic mothers at the beginning of gestation increased the risk of neurodevelopmental delay.	Pregnant woman, child

Grau et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Grau</Author><Year>2015</Year><RecNum>13</RecNum><DisplayText>(2015)</DisplayText><record><rec-number>13</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047634">13</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Grau, G</author><author>Aguayo, A</author><author>Vela, A</author><author>Aniel-Quiroga, A</author><author>Espada, M</author><author>Miranda, G</author><author>Martinez-Indart, L</author><author>Martul, P</author><author>Castaño, L</author><author>Rica, I</author></authors></contributors><titles><title>Normal intellectual development in children born from women with hypothyroxinemia during their pregnancy</title><secondary-title>Journal of Trace Elements in Medicine and Biology</secondary-title></titles><periodical><full-title>Journal of Trace Elements in Medicine and Biology</full-title></periodical><pages>18-24</pages><volume>31</volume><section>18</section><dates><year>2015</year></dates><urls></urls><electronic-resource-num>10.1016/j.jtemb.2015.02.004</electronic-resource-num></record></Cite></EndNote>] *Normal Intellectual Development in Children Born from Women with Hypothyroxinemia During Their Pregnancy*	455 Spanish mother-child pairs at age 1 assessment 289 Spanish mother-child pairs at age 6-8 assessment (1 yr 1st trimester cases = 47; 1 yr 2nd trimester cases = 42; 6-8 yr 1st trimester cases = 33; 6-8 yr 2nd trimester cases = 28)	fT4 < 10th percentile (< 13.7) (first trimester) fT4 < 10th percentile (11.5) (second trimester)	Neurocognitive performance *Brunet-Lézine scale*	Children of mothers with hypothyroxinemia in the first and second trimester from an iodine-sufficient area did not have adverse neurodevelopmental outcomes (assessed at age 1 with the Brunet-Lézine scale) associated with levels of fT4.	Pregnant woman
Hales et al. (2018)	331 mother-	fT4 < 2.5th percentile[c]	Child long-term	For women with	Pregnant woman

Controlled Antenatal Thyroid Screening II: Effect of Treating Maternal Sub-Optimal Thyroid Function on Child Cognition	child pairs from the UK (n_{cases} = 81; 40 of which were treated with thyroxine)		memory and motor function *Developmental Neuropsychological Assessment (NEPSY) second edition*	isolated hypothyroxinemia, there were no differences in mean scores were identified from NEPSY assessments (memory for designs; memory for designs delayed; fingertip tapping dominant hand; fingertip tapping non-dominant hand; narrative memory) (thyroxine treated n=38, untreated n=35, p=0.070)	

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
				and NEPSY - List Memory (treated n=30, untreated n=26, p=0.361).	

Päkkilä et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pakkila</Author><Year>2015</Year><RecNum>323</RecNum><DisplayText>(2015)</DisplayText><record><rec-number>323</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832494">323</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Päkkilä, F</author><author>Männistö, T</author><author>Hartikainen, A-L</author><author>Ruokonen, A. </author><author>et al.,</author></authors></contributors><titles><title>Maternal and child's thyroid function and child's intellect and scholastic performance</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>1363-1374</pages><volume>25</volume><number>12</number><dates><year>2015</year></dates><urls></urls><electronic-resource-num>10.1787/9789264091450-e</electronic-resource-num></record></Cite></EndNote>] *Maternal and Child's Thyroid Function and Child's Intellect and Scholastic Performance*	5,295 Finnish mother-child pairs with sufficient maternal serum samples (n_{cases} = 67)	fT4 < 11.4 in the first trimester fT4 < 11.1 in the second trimester[d]	Child School Performance *Teacher evaluation questionnaire and postal questionnaire (self-evaluation including the Youth Self-Report)*	Female offspring of mothers with subclinical hypothyroidism had more self-evaluated difficulties in mathematics than did females of mothers with thyroid function within the population reference range. Male offspring of hypothyroxinemic mothers repeated a school class more often than did males of mothers with normal thyroid function.	Pregnant woman, child

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
				Male offspring of hypothyroxinemic mothers also had a higher odds of having difficulties in Finnish and/or math.	

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
van Mil et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>van Mil</Author><Year>2012</Year><RecNum>45</RecNum><DisplayText>(2012)</DisplayText><record><rec-number>45</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437061977">45</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>van Mil, N.H.</author><author>Steegers-Theunissen, Regine P.M.</author><author>Bongers-Schokking, Jacoba J.</author><author>El Marroun, Hanan</author><author>Ghassabian, Akhgar</author><author>Hofman, Albert</author><author>Jaddoe, Vincent W.V.</author><author>Verhulst, Frank C.</author><author>de Rijke, Yolanda B.</author><author>Steegers, Eric A.P.</author><author>Tiemeier, Henning</author></authors></contributors><titles><title>Maternal hypothryoxinemia during pregnancy and growth of the fetal and infant head</title><secondary-title>Reproductive Sciences</secondary-title></titles><periodical><full-title>Reproductive Sciences</full-title></periodical><pages>1315-1322</pages><volume>19</volume><number>12</number><section>1315</section><dates><year>2012</year></dates><urls></urls><electronic-resource-num>10.1177/1933719112450338</electronic-resource-num></record></Cite></EndNote>] *Maternal Hypothyroxinemia During Pregnancy and Growth of the Fetal and Infant Head*	2,621 Dutch mother-child pairs (n_{cases} = 476)	fT4 < 10th percentile (11.82)	Fetal and infant head size *Sonography* Child cognitive development *Parent Report of Children Abilities*	Maternal hypothyroxinemia was associated with an increase in fetal head and infant head size. In addition, maternal hypothyroxinemia was associated with a statistically significant increased risk of cognitive delay.	Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Meta-Analysis					

Fan and Wu [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Fan</Author><Year>2016</Year><RecNum>307</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>307</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832068">307</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fan, X.</author><author>Wu, L.</author></authors></contributors><auth-address>a General Surgery Department and.
b Department of Obstetrics and Gynecology , Central People's Hospital of Siping , Siping , China.</auth-address><titles><title>The impact of thyroid abnormalities during pregnancy on subsequent neuropsychological development of the offspring: a meta-analysis</title><secondary-title>Journal of Maternal-Fetal & Neonatal Medicine</secondary-title></titles><periodical><full-title>Journal of Maternal-Fetal & Neonatal Medicine</full-title></periodical><pages>3971-6</pages><volume>29</volume><number>24</number><keywords><keyword>Hypothyroxinaemia</keyword><keyword>meta-analysis</keyword><keyword>neuropsychological development</keyword><keyword>pregnancy</keyword><keyword>subclinical hypothyroidism</keyword><keyword>thyroid peroxidase antibodies</keyword></keywords><dates><year>2016</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>1476-4954 (Electronic)
1476-4954 (Linking)</isbn><accession-num>26988121</accession-num><urls><related-urls><url><style face="underline" font="default" size="100%">http://www.ncbi.nlm.nih.gov/pubmed/26988121</style></url></related-urls></urls><electronic-resource-num>10.3109/14767058.2016.1152248</electronic-resource-num></record></Cite></EndNote>] *The Impact of Thyroid Abnormalities during Pregnancy on Subsequent Neuropsychological Development of the Offspring: A Meta-Analysis*	4,449 mother-child pairs identified through multiple studies. (n_{cases} = 310)[g]	Multiple studies evaluated, no set definition	Child Intelligence (IQ, Mental Development) *Weschler Intelligence Scale for Children or Bayley Scales of Infant Development*	Children born to hypothyroxinemic mothers had mean intelligence scores 5.7 points lower than non-hypothyroxinemic mothers. Children born to hypothyroxinemic mothers had mean motor scores 4.2 points lower than non-hypothyroxinemic mothers.	Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Thompson et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Thompson</Author><Year>2018</Year><RecNum>1956</RecNum><DisplayText>(2018)</DisplayText><record><rec-number>1956</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1516819485">1956</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Thompson, William</author><author>Russell, Ginny</author><author>Baragwanath, Genevieve</author><author>Matthews, Justin</author><author>Vaidya, Bijay</author><author>Thompson-Coon, Jo</author></authors></contributors><titles><title>Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis</title><secondary-title>Clinical endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><dates><year>2018</year></dates><isbn>1365-2265</isbn><urls></urls></record></Cite></EndNote>] *Maternal Thyroid Hormone Insufficiency during Pregnancy and Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-Analysis*	15,147 mother-child pairs identified through multiple studies[h]	Multiple studies evaluated, no set definition[i]	Child intellectual disability *Various - Multiple studies evaluated*	Compared to those children born to euthyroid mothers, children born to hypothyroxinemic mothers were significantly more likely to show signs of intellectual impairment (odds ratio (OR) 1.63, 95% CI 1.03 to 2.56, p=0.04).	Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Wang et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] *Maternal Thyroxine Levels During Pregnancy and Outcomes of Cognitive Development in Children*	8,273 mother-child pairs (n_{cases} = 702)[j]	Multiple studies evaluated, no set definition	Cognitive development *Various – multiple studies evaluated*	Meta-analysis showed low maternal fT4 level was significantly associated with increase in risk of delayed cognitive development in offspring.	Pregnant woman

[a] Some studies did not explicitly define hypothyroxinemia, and instead examined the impact of altered thyroid hormone levels below a defined percentile cut point and of altered neurodevelopment. For the purposes of this review, these percentile cut points are considered to be analogous to a definition for hypothyroxinemia.

[b] Pregnant woman: thyroid hormone measurement taken anytime during pregnancy. Fetus: thyroid hormone levels were measured from cord blood at birth. Neonate: thyroid hormone levels were measured from a source other than cord blood between birth and 28 days of age. Child: thyroid hormone levels were measured after 1 year of age.

[c] The value of the hypothyroxinemic cut point was not identified in the paper.

[d] Päkkilä et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pakkila</Author><Year>2015</Year><RecNum>323</RecNum><DisplayText>(2015)</DisplayText><record><rec-number>323</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832494">323</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Päkkilä, F</author><author>Männistö, T</author><author>Hartikainen, A-L</author><author>Ruokonen, A.</author><author>et al.,</author></authors></contributors><titles><title>Matemal and child's thyroid function and child's intellect and scholastic performance</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>1363-1374</pages><volume>25</volume><number>12</number><dates><year>2015</year></dates><urls></urls><electronic-resource-num>10.1787/9789264091450-e</electronic-resource-num></record></Cite></EndNote>] define hypothyroxinemia as "TSH within reference intervals with low fT4 concentrations" (p. 1365), but low fT4 is not defined. The lower range of the reference interval is 11.4 pmol/L for fT4 for the first trimester, and 11.09 pmol/L is the lower bound of the reference interval for the second trimester. These are assumed to be the cut points used to define low fT4.

[f] **Group 1:** fT4> 20th percentile at 4-6 gestational weeks and term, supplemented with 200 µg/day potassium iodine through term and lactation. Neurocognitive evaluation was done on children with mothers fT4>20th percentile at 4-6 weeks and at term. (n=13) **Group 2:** mildly hypothyroxinemic at 12-14 gestational weeks, supplemented with 200 µg/day potassium iodine through term and lactation. Neurocognitive evaluation done on children with maternal fT4 <10th percentile at 12-14 weeks and fT4>20th percentile at term (n=12) **Group 3:** enrolled at full term at which time they were supplemented with 200 µg/day potassium iodine throughout lactation. Neurocognitive evaluations were done on children born to a mother who had fT4<10th percentile at term. (n=18)

[g] The number of cases of hypothyroxinemia included in the Fan and Wu [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Fan</Author><Year>2016</Year><RecNum>307</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>307</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832068">307</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fan, X.</author><author>Wu, L.</author></authors></contributors><auth-address>a General Surgery Department and.
b Department of Obstetrics and Gynecology , Central People's Hospital of Siping , Siping , China.</auth-address><titles><title>The impact of thyroid abnormalities during pregnancy on subsequent neuropsychological development of the offspring: a meta-analysis</title><secondary-title>Journal of Maternal-Fetal & Neonatal Medicine</secondary-title></titles><periodical><full-title>Journal of Maternal-Fetal & Neonatal Medicine</full-title></periodical><pages>3971-6</pages><volume>29</volume><number>24</number><keywords><keyword>Hypothyroxinaemia</keyword><keyword>meta-analysis</keyword><keyword>neuropsychological development</keyword><keyword>pregnancy</keyword><keyword>subclinical hypothyroidism</keyword><keyword>thyroid peroxidase antibodies</keyword></keywords><dates><year>2016</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>1476-4954 (Electronic)
1476-4954 (Linking)</isbn><accession-num>26988121</accession-num><urls><related-urls><url><style face="underline" font="default" size="100%">http://www.ncbi.nlm.nih.gov/pubmed/26988121</style></url></related-urls></urls><electronic-resource-num>10.3109/14767058.2016.1152248</electronic-resource-num></record></Cite></EndNote>] meta-analysis are summed from Table 1 of the paper. All cases used in the pooled analysis, including subclinical hypothyroidism, sum to 397 women.

[h] The number of cases of hypothyroxinemia included in the Thompson et al. (2018) meta-analysis are summed from Supplementary Table 1 of the paper. Cases in the pooled analysis were not identified.

[i] Where multiple cut points of TSH and fT4 were measured, the most extreme cutoff was used, and when an outcome was measured both against a continuous thyroid hormone measure and against a cut point (for example, cut point of the 10th percentile fT4 for hypothyroxinemia), the cut point was used.

[j] The number of cases with hypothyroxinemia was determined from Table 1 of the paper and by deriving values from within individual studies if the number of cases was not indicated.

Table [SEQ Table * ARABIC]. Overview of Studies Categorized as Group 2 – Behavior (Including ADHD)

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]

Ghassabian, Henrichs, and Tiemeier [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2014</Year><RecNum>11</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>11</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047632">11</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A</author><author>Henrichs, J</author><author>Tiemeier, H</author></authors></contributors><titles><title>Impact of mild thyroid hormone deficiency in pregnancy on cognitive function in children: lessons from the Generation R Study</title><secondary-title>Best Practice & Research and Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>Best Practice & Research and Clinical Endocrinology & Metabolism</full-title></periodical><pages>221-232</pages><volume>28</volume><number>2</number><section>221</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1016/j.beem.2013.04.008</electronic-resource-num></record></Cite></EndNote>] *Impact of Mild Thyroid Hormone Deficiency in Pregnancy on Cognitive Function in Children: Lessons from the Generation R Study*	3,903 Dutch mother-child pairs (n_{cases} = 129)	Severe: fT4 < 5th or 10th percentile of sample (exact value not defined)	ADHD Problems *Child Behavior Checklist for Toddlers*	This paper reviews the literature from the Generation R cohort and presents novel results related to ADHD and maternal hypothyroxinemia. They found maternal hypothyroxinemia to be associated with ADHD problems with some of the association attenuated when considering maternal factors such as	Fetus, Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
				age and education level. The review also summarizes results presented in Henrichs et al. (2010), van Mil et al. (2012), Ghassabian et al. (2011), and Ghassabian et al. (2012).	

Kooistra, Crawford, van Baar, Brouwers, and Pop [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Kooistra</Author><Year>2006</Year><RecNum>47</RecNum><DisplayText>(2006)</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437065646">47</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kooistra, L</author><author>Crawford, S</author><author>van Baar, A L</author><author>Brouwers, E</author><author>Pop, V</author></authors></contributors><titles><title>Neonatal effects of maternal hypothyroxinemia during early pregnancy</title><secondary-title>Pediatrics</secondary-title></titles><periodical><full-title>Pediatrics</full-title></periodical><pages>161-167</pages><volume>117</volume><number>1</number><section>161</section><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>] *Neonatal Effects of Maternal Hypothyroxinemia During Early Pregnancy*	204 Dutch mother-child pairs (n_{cases} = 108)	fT4 < 10th percentile (< 10.4)	Neonatal Development *Neonatal Behavioral Assessment Scale*	Infants of women with hypothyroxinemia at GW 12 had a lower neonatal Behavioral Assessment Scale orientation index compared with infants of non-hypothyroxinemic women. Neonatal thyroid hormone levels were not assessed in regard to neurodevelopment.	Neonate, pregnant woman
Päkkilä et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Päkkilä</Author><Year>2014</Year><RecNum>23</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>23</rec-number><foreign-	5,131 Finnish mothe	fT4 < 11.4 in the first trimester	Child ADHD	Maternal hypothyroxinemia was not	Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047640">23</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Päkkilä, F</author><author>Männistö, T</author><author>Pouta, A</author><author>Hartikainen, A</author><author>Ruokonen, A</author><author>Surcel, H</author><author>Bloigu, A</author><author>Vääräsmäki, M</author><author>Järvelin, M</author><author>Moilanen, I</author><author>Suvanto, E</author></authors></contributors><titles><title>The impact of gestational thyroid hormone concentrations on ADHD symptoms of the child</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>E1-E8</pages><volume>99</volume><number>1</number><section>E1</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2013-2943</electronic-resource-num></record></Cite></EndNote>] *The Impact of Gestational Thyroid Hormone Concentration on ADHD Symptoms of the Child*	r-child pairs (n_{cases} = 66)	fT4 < 11.1 in the second trimester	*Finnish translations of the Rutter scale B2*	significantly associated with teacher ratings of ADHD symptoms in children at 8 years of age.	

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Meta-Analysis					
Thompson et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Thompson</Author><Year>2018</Year><RecNum>1956</RecNum><DisplayText>(2018)</DisplayText><record><rec-number>1956</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1516819485">1956</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Thompson, William</author><author>Russell, Ginny</author><author>Baragwanath, Genevieve</author><author>Matthews, Justin</author><author>Vaidya, Bijay</author><author>Thompson-Coon, Jo</author></authors></contributors><titles><title>Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis</title><secondary-title>Clinical endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><dates><year>2018</year></dates><isbn>1365-2265</isbn><urls></urls></record></Cite></EndNote>] *Maternal Thyroid Hormone Insufficiency during Pregnancy and Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-Analysis*	15,147 mother-child pairs identified through multiple studies[c]	Multiple studies evaluated, no set definition[d]	ADHD *Various - Multiple studies evaluated*	No association was found between maternal hypothyroxinemia and ADHD in children (OR 1.34, 95% CI 0.17 to 10.47, p=0.78).	Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]

[a] Some studies did not explicitly define hypothyroxinemia, and instead examined the impact of altered thyroid hormone levels below a defined percentile cut point and of altered neurodevelopment. For the purposes of this review, these percentile cut points are considered to be analogous to a definition for hypothyroxinemia.

[b] Pregnant woman: thyroid hormone measurement taken anytime during pregnancy. Fetus: thyroid hormone levels were measured from cord blood at birth. Neonate: thyroid hormone levels were measured from a source other than cord blood between birth and 28 days of age. Child: thyroid hormone levels were measured after 1 year of age.

[c] The number of cases of hypothyroxinemia included in the Thompson et al. (2018) meta-analysis are summed from Supplementary Table 1 of the paper. Cases in the pooled analysis were not identified.

[d] Where multiple cut points of TSH and fT4 were measured, the most extreme cut point was used, and when an outcome was measured both against a continuous thyroid hormone measure and against a cut point (for example, cut point of the 10th percentile fT4 for hypothyroxinemia), the cut point was used.

Table [SEQ Table * ARABIC]. Overview of Studies Categorized as Group 2 – Autism

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Brown et al. (2015) *Maternal Thyroid Autoantibody and Elevated Risk of Autism in a National Birth Cohort*	1,916 Finnish mother-child pairs mothers with fT4 (n_{cases} = 958; cases defined as being diagnosed with autism)	None	Autism *Recorded diagnosis from psychiatric hospital admissions and outpatient visits of childhood autism*	There was no association found between maternal fT4 and autism (cases, mean maternal fT4 (SD) 14.7 (2.0); comparison subjects, mean (SD) = 14.7 (1.92)) OR = 1.09 (95%CI 0.52-12.26, *p* =0.83)	Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Meta-Analysis					

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]
Thompson et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Thompson</Author><Year>2018</Year><RecNum>1956</RecNum><DisplayText>(2018)</DisplayText><record><rec-number>1956</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1516819485">1956</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Thompson, William</author><author>Russell, Ginny</author><author>Baragwanath, Genevieve</author><author>Matthews, Justin</author><author>Vaidya, Bijay</author><author>Thompson-Coon, Jo</author></authors></contributors><titles><title>Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis</title><secondary-title>Clinical endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><dates><year>2018</year></dates><isbn>1365-2265</isbn><urls></urls></record></Cite></EndNote>] *Maternal Thyroid Hormone Insufficiency during Pregnancy and Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-Analysis*	15,147 mother-child pairs identified through multiple studies[c]	Multiple studies evaluated, no set definition[d]	Autism *Various - Multiple studies evaluated*	Of two studies identified, a study that used a continuous predictor (i.e., maternal fT4) found no association between maternal hypothyroxinemia and autism, but the other study that used a binary predictor (i.e., maternal hypothyroxinemia) did.	Pregnant woman

Study	Population Analyzed for Key Findings	Definition of Hypothyroxinemia (pmol/L, unless otherwise noted)[a]	Endpoint(s) | *Test(s)*	Summary of Key Findings	Life Stage of Thyroid Hormone Measurement[b]

[a] Some studies did not explicitly define hypothyroxinemia, and instead examined the impact of altered thyroid hormone levels below a defined percentile cut point and of altered neurodevelopment. For the purposes of this review, these percentile cut points are considered to be analogous to a definition for hypothyroxinemia.

[b] Pregnant woman: thyroid hormone measurement taken anytime during pregnancy. Fetus: thyroid hormone levels were measured from cord blood at birth. Neonate: thyroid hormone levels were measured from a source other than cord blood between birth and 28 days of age. Child: thyroid hormone levels were measured after 1 year of age.

[c] The number of cases of hypothyroxinemia included in the Thompson et al. (2018) meta-analysis are summed from Supplementary Table 1 of the paper. Cases in the pooled analysis were not identified.

[d] Where multiple cut points of TSH and fT4 were measured, the most extreme cut point was used, and when an outcome was measured both against a continuous thyroid hormone measure and against a cut point (for example, cut point of the 10th percentile fT4 for hypothyroxinemia), the cut point was used.

Of the 15 papers identified as Group 2, 11 evaluated cognitive outcomes [ADDIN EN.CITE ADDIN EN.CITE.DATA], four evaluated behavioral outcomes [ADDIN EN.CITE ADDIN EN.CITE.DATA] and two evaluated autism [ADDIN EN.CITE ADDIN EN.CITE.DATA] as they relate to maternal thyroid hormone dysfunction, most often defined as maternal hypothyroxinemia (Thompson et al. (2018) evaluated all three categories of endpoints and is thus included in each count listed and in each table). Of the cognition studies, there were consistent results associating maternal hypothyroxinemia with decreased performance on the Bayley Scales. None of the Group 2 studies evaluated found a significant difference in IQ when comparing results in offspring of mother with hypothyroxinemia to those of mothers without hypothyroxinemia. However, three meta-analyses (including one full systematic review, Thompson et al., 2018) conclude that maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests [ADDIN EN.CITE ADDIN EN.CITE.DATA]. These review papers evaluated studies that are included in Groups 1, 2, and 3 of this analysis and subsequently provide a more comprehensive understanding of the relationship between maternal hypothyroxinemia and altered cognitive development in offspring.

The three non-review studies that evaluated behavioral outcomes (Ghassabian, Henrichs, and Tiemeier, 2014; Kooistra, Crawford, van Baar, Brouwers, and Pop, 2006; Päkkilä et al., 2014) found mixed evidence relating maternal hypothyroxinemia with increased risk of ADHD or decreased scores on behavioral assessment tests. Thompson et al. (2018) did not find an association between maternal hypothyroxinemia and ADHD.

Lastly, one independent study (Brown et al., 2015) and one review paper (Thompson et al., 2018) were categorized as Group 2 and evaluated maternal hypothyroxinemia as associated with autism. Brown et al. (2015) did not find an association. Thompson et al. (2018) concluded that the association between maternal hypothyroxinemia and autism was uncertain.

Brief descriptions of all studies are presented in Appendix G.

Summary of Group 1 Studies

After categorizing 15 studies in Group 2, 16 remained to be categorized as Group 1. The EPA focused on this set of 16 studies due to the presence of an analysis that evaluated maternal fT4 as a continuous variable, as it related to offspring neurodevelopment. Group 1 includes studies that found statistically significant changes and those that did not. In many but not all of these studies the general results, though not statistically significant, were consistent with the studies used for further quantitative analyses by the EPA. The EPA presents and characterizes all of the Group 1 studies below.

Studies categorized in Group 1 present data that may allow for the extraction of a function relating a continuous measure of thyroid hormone levels to some measure of neurodevelopment. In combination with the BBDR model, this function may be used to identify the dose of perchlorate associated with a defined change in neurodevelopment. Several of the studies in this group did not include an estimated regression function, but instead presented a scatterplot that depicts a regression or correlation analysis.[11] The graphical data presented in these studies was digitized to allow for the estimation of a

[11] The authors of each of these studies were contacted from July 2015 to February 2017 to determine if they have the underlying data for these figures. The EPA has not received responses from many of the authors as of the date of release of this document.

function. The papers categorized as Group 1 are summarized in [REF _Ref491174324 \h] in Section [REF _Ref492391106 \n \h], including findings related to the continuous relationship presented in the paper and information necessary to evaluate the papers as outlined above in Step 3. Many of these papers present regression analyses on more than one endpoint or age group. The majority of the continuous relationships presented pertain to the entire range of maternal fT4 and are not specific to just the offspring of hypothyroxinemic mothers. However, many of the Group 1 studies also present a categorical analysis comparing neurodevelopmental outcomes in the offspring of hypothyroxinemic and non-hypothyroxinemic mothers; this is discussed further in Section [REF _Ref482275380 \r \h]. To facilitate a better understanding of the relationship between maternal thyroid hormones and the neurodevelopmental outcomes, the study summaries have been grouped into four categories: cognitive (including IQ, Bayley Scales, and other measures), behavior (including ADHD and others), autism, and other endpoints not otherwise captured.

Cognitive (IQ)

Detailed Summary of Ghassabian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2014</Year><RecNum>10</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047632">10</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A</author><author>Marroun, H E</author><author>Peeters, R P</author><author>Jaddoe, V W</author><author>Hofman, A</author><author>Verhulst, F C</author><author>Tiemeier, H</author><author>White, T</author></authors></contributors><titles><title>Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2383-2390</pages><volume>99</volume><number>7</number><section>2383</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2013-4281</electronic-resource-num></record></Cite></EndNote>]

Downstream Effects of Maternal Hypothyroxinemia in Early Pregnancy: Nonverbal IQ and Brain Morphology in School-Age Children

Ghassabian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2014</Year><RecNum>10</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047632">10</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A</author><author>Marroun, H E</author><author>Peeters, R P</author><author>Jaddoe, V W</author><author>Hofman, A</author><author>Verhulst, F C</author><author>Tiemeier, H</author><author>White, T</author></authors></contributors><titles><title>Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2383-2390</pages><volume>99</volume><number>7</number><section>2383</section><dates><year>

2014</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2013-4281</electronic-resource-num></record></Cite></EndNote>] aimed to examine whether children born to mothers with hypothyroxinemia during early pregnancy would show decreased nonverbal IQ at 6 years of age. Along with reductions in IQ, Ghassabian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2014</Year><RecNum>10</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047632">10</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A</author><author>Marroun, H E</author><author>Peeters, R P</author><author>Jaddoe, V W</author><author>Hofman, A</author><author>Verhulst, F C</author><author>Tiemeier, H</author><author>White, T</author></authors></contributors><titles><title>Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2383-2390</pages><volume>99</volume><number>7</number><section>2383</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2013-4281</electronic-resource-num></record></Cite></EndNote>] hypothesized that children of hypothyroxinemic mothers would display corresponding structural changes in the size of several key areas of the brain: the cortex, hippocampus, and corpus callosum. An additional aim was to investigate the relationship between subclinical hypothyroidism (normal fT4 and high TSH) in mothers and IQ in children. Participants (n = 3,727) were recruited from the Generation R birth cohort in the Netherlands; all singleton births with complete information on maternal thyroid levels and children's nonverbal IQ at age 6 were included in the study. A subset of children participating in the study (n = 652) underwent magnetic resonance imaging (MRI) testing to assess volume of various brain regions. Maternal thyroid function (fT4, TSH, and TPO Ab) were measured at a mean of 13.5 GW. Hypothyroxinemia was defined as fT4 levels below 10.99 pmol/L (the 5th percentile of the sample) and subclinical hypothyroidism as normal fT4 and high TSH (defined as TSH > 2.5 mIU/L or > 3.0 mIU/L). Children completed a well-validated Dutch nonverbal intelligence test (the Snijders-Oomen Niet-Verbale Intelligentie test), which consisted of Mosaics to assess spatial visualization skills and Categories to assess abstract reasoning skills. Linear regression models were used to investigate the association between maternal thyroid function and children's nonverbal IQ and brain volumetric measures. Maternal fT4 and TSH were divided by their SD in the regression analyses to determine the impact of SD increments or decrements in these parameters. Regression analyses with IQ as the outcome were adjusted for ethnicity, birth order, maternal age, BMI, marital status, maternal history of smoking, educational levels, maternal psychopathology during pregnancy, household income, and gestational age at time of thyroid sampling.

Ghassabian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2014</Year><RecNum>10</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047632">10</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A</author><author>Marroun, H E</author><author>Peeters, R P</author><author>Jaddoe, V W</author><author>Hofman, A</author><author>Verhulst, F C</author><author>Tiemeier, H</author><author>White,

T</author></authors></contributors><titles><title>Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2383-2390</pages><volume>99</volume><number>7</number><section>2383</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2013-4281</electronic-resource-num></record></Cite></EndNote>] did not find an association between continuous measures of maternal thyroid function (fT4, TSH, and TPO Ab positivity) and children's IQ at the age of 6 years. An analysis of continuous fT4 and its relationship with IQ in just the children of hypothyroxinemic mothers was not conducted. However, Ghassabian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2014</Year><RecNum>10</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047632">10</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A</author><author>Marroun, H E</author><author>Peeters, R P</author><author>Jaddoe, V W</author><author>Hofman, A</author><author>Verhulst, F C</author><author>Tiemeier, H</author><author>White, T</author></authors></contributors><titles><title>Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2383-2390</pages><volume>99</volume><number>7</number><section>2383</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2013-4281</electronic-resource-num></record></Cite></EndNote>] did find that children of mothers with hypothyroxinemia scored an average of 4.3 IQ points lower ($p = 0.001$, 95% CI: -6.68, -1.81) on IQ tests than children of mothers with thyroid function within the population reference range. No significant associations were found between maternal hypothyroxinemia and any of the brain volume measures assessed. Maternal subclinical hypothyroidism did not show a significant relationship with children's IQ. A summary of results can be found in [REF _Ref517338346 \h].

Table [SEQ Table * ARABIC]. Summary of Results from Ghassabian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2014</Year><RecNum>10</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047632">10</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A</author><author>Marroun, H E</author><author>Peeters, R P</author><author>Jaddoe, V W</author><author>Hofman, A</author><author>Verhulst, F C</author><author>Tiemeier, H</author><author>White, T</author></authors></contributors><titles><title>Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2383-2390</pages><volume>99</volume><number>7</number><section>2383</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2013-4281</electronic-resource-num></record></Cite></EndNote>]

Maternal Thyroid Function	Child's IQ at 6 years of age		
	β	95% CI	*p*-value
TSH per SD	0.04	-0.17, 0.26	0.70
fT4 per SD	-0.24	-0.61, 0.14	0.21
Hypothyroxinemia	-4.32	-6.68, -1.81	**0.001**

Source: Ghassabian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2014</Year><RecNum>10</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047632">10</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A</author><author>Marroun, H E</author><author>Peeters, R P</author><author>Jaddoe, V W</author><author>Hofman, A</author><author>Verhulst, F C</author><author>Tiemeier, H</author><author>White, T</author></authors></contributors><titles><title>Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2383-2390</pages><volume>99</volume><number>7</number><section>2383</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2013-4281</electronic-resource-num></record></Cite></EndNote>], Table 2.
Models were adjusted for child's ethnic background and birth order and maternal age, BMI, marital status, maternal history of smoking, educational levels, maternal psychopathology in pregnancy, household income, and time of blood sampling in pregnancy.
Hypothyroxinemia (n = 129): 0.03 < TSH < 2.5 mIU/L and fT4 < 10.99 pmol/L (less than the 5th percentile).

Key Finding: Maternal hypothyroxinemia during early pregnancy (mean GW = 13.5) was associated with an average reduction of 4.3 points ($p = 0.001$, 95% CI: -6.68, -1.81) in children's nonverbal IQ at age 6. Continuous measures of maternal thyroid function (TSH, fT4) across the entire range (not the hypothyroxinemic range) and subclinical hypothyroidism were not significantly associated with nonverbal IQ in 6-year-old children.

Detailed Summary of Korevaar et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Korevaar</Author><Year>2016</Year><RecNum>313</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>313</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832236">313</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, Tim I. M.</author><author>Muetzel, Ryan</author><author>Medici, Marco</author><author>Chaker, Layal</author><author>Jaddoe, Vincent W. V.</author><author>de Rijke, Yolanda B.</author><author>Steegers, Eric A. P.</author><author>Visser, Theo J.</author><author>White, Tonya</author><author>Tiemeier, Henning</author><author>Peeters, Robin P.</author></authors></contributors><titles><title>Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study</title><secondary-title>The Lancet Diabetes & Endocrinology</secondary-title></titles><periodical><full-title>The Lancet Diabetes & Endocrinology</full-title></periodical><pages>35-43</pages><volume>4</volume><number>1</number><dates><year>2016</year></dates><isbn>22138587</isbn><urls></urls><electronic-resource-num>10.1016/s2213-8587(15)00327-7</electronic-resource-num></record></Cite></EndNote>]

Association of Maternal Thyroid Function during Early Pregnancy with Offspring IQ and Brain Morphology in Childhood: A Population-Based Prospective Cohort Study

Korevaar et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Korevaar</Author><Year>2016</Year><RecNum>313</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>313</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832236">313</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, Tim I. M.</author><author>Muetzel, Ryan</author><author>Medici, Marco</author><author>Chaker, Layal</author><author>Jaddoe, Vincent W. V.</author><author>de Rijke, Yolanda B.</author><author>Steegers, Eric A. P.</author><author>Visser, Theo J.</author><author>White, Tonya</author><author>Tiemeier, Henning</author><author>Peeters, Robin P.</author></authors></contributors><titles><title>Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study</title><secondary-title>The Lancet Diabetes & Endocrinology</secondary-title></titles><periodical><full-title>The Lancet Diabetes & Endocrinology</full-title></periodical><pages>35-43</pages><volume>4</volume><number>1</number><dates><year>2016</year></dates><isbn>22138587</isbn><urls></urls><electronic-resource-num>10.1016/s2213-8587(15)00327-7</electronic-resource-num></record></Cite></EndNote>] examined the relationship between maternal thyroid function, child IQ, and brain morphology. Maternal thyroid function data, including TSH, fT4, and TPO Ab, were assessed at 9-18 weeks of pregnancy. Child IQ was assessed between 5.6 and 7.9 years of age using a Dutch non-verbal intelligence test with high reliability (the Snijders-Oomen Niet-Verbale Intelligentie Test). The IQ test assesses a broad range of language-independent intelligence functions such as spatial visualization abilities and abstract reasoning abilities. Child brain morphology was assessed using structural MRI brain scans. Pregnant mothers were recruited if

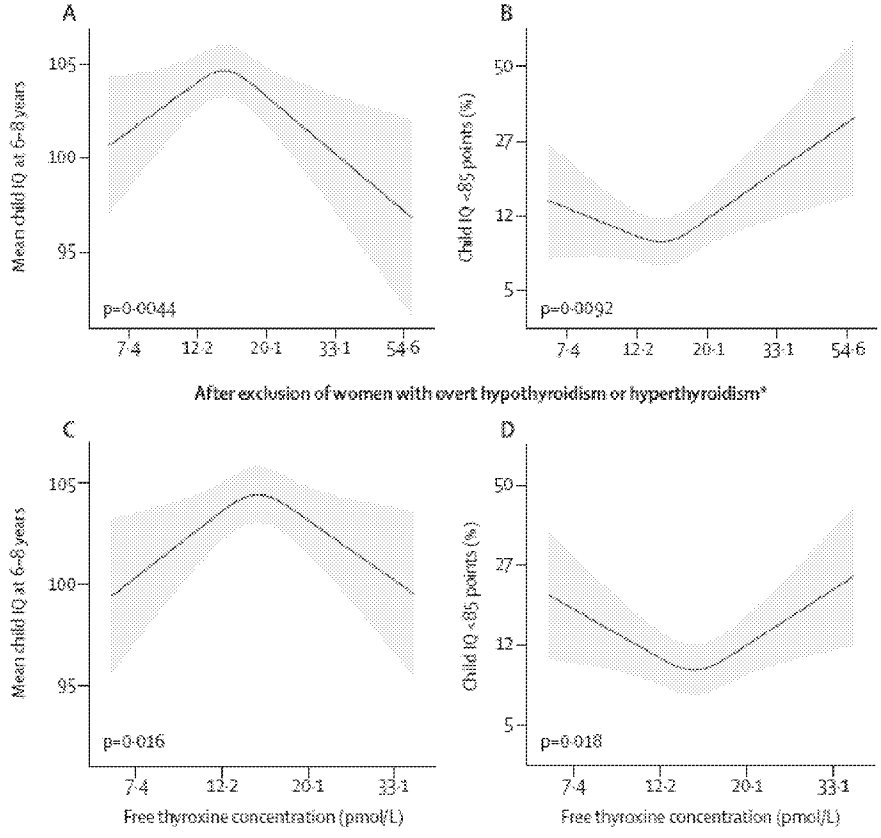
they lived in the municipality of Rotterdam, Netherlands, and were enrolled as participants in the Generation R Study. The main exclusion criteria for mother-child pairs were abortion, fetal loss, or gestational age of 24 weeks or more at the start of the study. Additional exclusion criteria for mother-child pairs undergoing the IQ assessment were twin pregnancies, pre-existing thyroid disease, concomitant medication that affects thyroid function, fertility treatment, or IQ scores ≤ 50. After exclusion criteria were applied, 3,839 mother-child pairs constituted the IQ study population, and 646 were included in the brain morphology study population (598 mother-child pairs overlapped between the two analyses). TSH and fT4 were log-transformed and then evaluated for associations with child IQ or brain morphology MRI outcomes using ordinary least-squares linear regression models with restricted cubic splines with knots at the 10th, 50th, and 90th percentiles. Effect estimates were reported from multivariate linear regression models with a quadratic term that approximated the model curves developed in the spline analysis. In analyses of IQ, models were adjusted for potential confounders including gestational age, maternal age, smoking, BMI, parity, education level, ethnic origin, fetal sex, and birthweight. Analyses of brain morphology were adjusted for gestational age, maternal age, BMI, child age, sex, birthweight, and gestational age at birth. All analyses were adjusted for hCG, TPO Ab, and child thyroid function.

Selected study results are included in [REF _Ref474405694 \h * MERGEFORMAT]. Overall, analysis results between maternal fT4 and offspring IQ showed an inverted U-shaped association (p = 0.0044 in the whole population ([REF _Ref474405694 \h * MERGEFORMAT] A); p = 0.016 after exclusion of women with overt hypothyroidism or hyperthyroidism ([REF _Ref474405694 \h * MERGEFORMAT] C)). All associations remained similar after adjusting for concentrations of hCG, child TSH and fT4, or maternal TPO Ab. Associations remained significant after the exclusion of cases of overt hypothyroidism and overt hyperthyroidism, which implies that changes in fT4 in the subclinical range can affect IQ (Korevaar et al., 2016). Korevaar et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Korevaar</Author><Year>2016</Year><RecNum>313</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>313</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832236">313</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, Tim I. M.</author><author>Muetzel, Ryan</author><author>Medici, Marco</author><author>Chaker, Layal</author><author>Jaddoe, Vincent W. V.</author><author>de Rijke, Yolanda B.</author><author>Steegers, Eric A. P.</author><author>Visser, Theo J.</author><author>White, Tonya</author><author>Tiemeier, Henning</author><author>Peeters, Robin P.</author></authors></contributors><titles><title>Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study</title><secondary-title>The Lancet Diabetes & Endocrinology</secondary-title></titles><periodical><full-title>The Lancet Diabetes & Endocrinology</full-title></periodical><pages>35-43</pages><volume>4</volume><number>1</number><dates><year>2016</year></dates><isbn>22138587</isbn><urls></urls><electronic-resource-num>10.1016/s2213-8587(15)00327-7</electronic-resource-num></record></Cite></EndNote>] found that the relationship demonstrated in the spline model ([REF _Ref474405694 \h]) was well explained by the multivariate linear regression analysis with a quadratic term, as summarized in [REF _Ref479341381 \h].

Further, high maternal fT4 (range of cut points: > 88th to > 97th percentile) corresponded to a 1.4 to 3.7 point reduction in mean offspring IQ when compared to the reference group (fT4 between 10th and 90th percentile). Low maternal fT4 (range of cut points: < 3rd to < 11th) corresponded to a 1.5 to 3.8 point loss when compared to the reference group.

For the MRI portion of the study, associations with maternal fT4 showed a U-shaped association for mean child gray matter volume ($p = 0.0062$ in the whole population; $p = 0.011$ after exclusion of women with overt hypothyroidism or hyperthyroidism) and for mean cortex volume ($p = 0.0011$ in the whole population; $p = 0.0016$ after exclusion of women with overt hypothyroidism or hyperthyroidism).

Figure [SEQ Figure * ARABIC]. Association between Maternal Free Thyroxine and Offspring IQ



(A, C) Association between maternal fT4 concentrations during pregnancy and child IQ as predicted mean and 95% CI in the whole population (A) and after the exclusion of women with overt thyroid disease (C). (B, D) Association of maternal fT4 levels during pregnancy and the risk of child IQ below 85 as predicted by back-transformed log odds with 95% CI in the whole population (B) and after the exclusion of women with overt thyroid disease (D). Scales for the x-axis might differ between the upper and lower graphs because of exclusions of women with overt, but not subclinical, disease entities. *Overt hypothyroidism and hyperthyroidism are defined as the biochemical diagnosis made during pregnancy, based on the central 95% reference range, as advocated in international guidelines (Korevaar et al., 2016).

Table [SEQ Table * ARABIC]. Summary of Results Evaluating the Relationship Between Maternal fT4 Levels with Mean Child IQ

Variables in Model	IQ: β (95% CI) [b]
fT4	33.81 (9.8, 57.82) [a]
$fT4^2$	-6.235 (-10.567, -1.903) [a]

Source: Korevaar et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Korevaar</Author><Year>2016</Year><RecNum>313</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>313</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832236">313</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, Tim I. M.</author><author>Muetzel, Ryan</author><author>Medici, Marco</author><author>Chaker, Layal</author><author>Jaddoe, Vincent W. V.</author><author>de Rijke, Yolanda B.</author><author>Steegers, Eric A. P.</author><author>Visser, Theo J.</author><author>White, Tonya</author><author>Tiemeier, Henning</author><author>Peeters, Robin P.</author></authors></contributors><titles><title>Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study</title><secondary-title>The Lancet Diabetes & Endocrinology</secondary-title></titles><periodical><full-title>The Lancet Diabetes & Endocrinology</full-title></periodical><pages>35-43</pages><volume>4</volume><number>1</number><dates><year>2016</year></dates><isbn>22138587</isbn><urls></urls><electronic-resource-num>10.1016/s2213-8587(15)00327-7</electronic-resource-num></record></Cite></EndNote>].

[a] Statistically significant at $p<0.05$.

[b] Reported beta and 95% confidence interval are increase in IQ per log increase in fT4. 95% confidence intervals were calculated by multiplying standard error of 12.25 for fT4 and 2.210 for $fT4^2$ presented in Korevaar et al. (2016) by 1.96. $fT4^2$ refer to addition of a squared fT4 variable in the model. Analyses were performed using linear regression models in N=3,839 mother-child pairs. fT4 values were transformed by the natural logarithm.

Key finding: The authors concluded that both low and high maternal fT4 concentrations during pregnancy were associated with lower child IQ and lower gray matter and cortex volume.

Detailed Summary of Moleti et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA]

Effects of Maternal Iodine Nutrition and Thyroid Status on Cognitive Development in Offspring: A Pilot Study

Moleti et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] examined the effects of maternal iodine and/or levothyroxine (LT4) supplementation on the IQ of their offspring. This prospective, observational study included four study groups of 15 mother-child pairs from a small, rural area in northeastern Sicily. The groups were iodine (I); no iodine (no-I); iodine + LT4 (I + T4); and no iodine + LT4 (no-I + T4). Pregnant mothers were sampled for fT3, fT4, TSH, TPO Ab (considered positive if values > 34 IU/mL), and antithyroglobulin (TgAb) starting at GW < 12 weeks and continuing every 6 weeks throughout pregnancy. To be included in the iodine groups, women had to have regularly consumed iodized salt up to 2 years prior to pregnancy and continued consumption during pregnancy. For the no-iodine groups, women were excluded if they had regular iodized salt consumption prior to pregnancy or consumed iodized salt upon becoming pregnant. Other inclusion criteria for mothers included age greater than 18 years, an uncomplicated singleton pregnancy, (full) term delivery, no severe or chronic diseases (including thyroid autoimmune diseases), no major post-partum complications, and full disclosure of diet and lifestyle information during and after pregnancy.

Inclusion criteria for children included age 6 to 14 years, no major neonatal complications, no congenital hypothyroidism, no severe/chronic diseases or cognitive deficits, and regular school attendance. Children ages 6 to 12 years of age were administered IQ tests blind by trained psychologists with the WISC-III, full-scale IQ (FSIQ), verbal IQ, and performance IQ (PIQ). FSIQ scores of 70-85 were considered suggestive of borderline defective cognitive function, and scores less than 70 were considered suggestive of defective cognitive function.

Statistical analyses were performed using the Mann-Whitney (comparison of independent samples), Wilcoxon (comparison of dependent samples), and Friedman (comparison over the observation period of several dependent groups) tests. A chi-squared (χ^2) test was used to evaluate the association between categorical variables. Logistic regression models were used to evaluate the dependence of suboptimal cognitive outcomes (IQ scores less than 85) on various explanatory variables and confounders. Covariates assessed in the models included maternal age; gestational age at birth; birthweight; child age at time of IQ test; maternal fT4, and TSH at various times during gestation; maternal urinary iodide excretion; family socioeconomic status; maternal parity; sex of child; breastfeeding; major maternal stressful life events; and maternal/parental education.

Overall, mothers in the iodine groups had significantly higher fT4 concentrations than those in the no-iodine groups. In this study, fT4 was evaluated across the entire range of pregnancy and fT4 concentrations, and not solely the hypothyroxinemic range in early pregnancy. The overall prevalence of borderline or defective cognitive function was more than three-fold higher in offspring of mothers not using iodized salt compared to mothers using it (76.9% vs. 23.1%, OR = 7.667, 95% CI: 2.365-24.856; $\chi^2 = 12.65$; $p = 0.0001$). Children born to mothers in the iodine group had significantly higher FSIQ and verbal IQ (VIQ) scores compared to the no-iodine offspring (FSIQ: (I) 93.1 ± 11.8 vs. (no-I) 81.7 ± 13.5, $p = 0.028$; VIQ (I) 90.1 ± 14.2 vs. (no-I) 80.3 ± 12.3, $p = 0.034$). Similar differences were found between I + T4 and no-I + T4 offspring. The relationship between fT4 at various periods of gestation was consistently associated with verbal, performance, and FSIQ, but failed to reach statistical significance ([REF _Ref475454870 \h * MERGEFORMAT]). Given the small sample size in the study, the authors caution against firm conclusions being drawn from their analysis. Additionally, the design of the study did not include parental IQ testing (a possible confounder for child IQ). The hypothesis set forward by the authors for the results of their analysis, which show iodine to be a more important predictor of neurodevelopmental outcomes compared to thyroid hormone levels, is that the fetus is exposed to insufficient amounts of thyroid hormone as a result of not having enough iodine from the mother to develop its own thyroid hormones.

Table [SEQ Table * ARABIC]. Relationship Between Cognitive Outcomes and fT4 (Univariate Logistic Regression Models)

	VIQ: exp β (95% CI)	PIQ: exp β (95% CI)	FSIQ: exp β (95% CI)
Gestational Weeks of fT4 Measurement			
≤12 weeks	1.192 (0.980-1.450)	1.053 (0.881-1.259)	1.103 (0.928-1.311)
13 - 18 weeks	1.217 (1.015-1.459)[a]	1.010 (0.855-1.194)	1.165 (0.980-1.385)
19 - 24 weeks	1.234 (0.991-1.537)	1.125 (0.897-1.411)	1.155 (0.937-1.425)
25 - 30 weeks	1.137 (0.928-1.393)	1.003 (0.810-1.243)	1.031 (0.847-1.254)
Week 31 - term	1.191 (0.982-1.445)	1.010 (0.834-1.224)	1.070 (0.895-1.280)
Maternal Urinary Iodide Concentration			
	1.017 (1.001-1.033)[b]	1.012 (0.995-1.028)	1.013 (0.998-1.029)

Source: Moleti et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA].
[a] 95% CI interval suggests statistical significance, but significance for this result and most results in this table were not denoted in the study.
[b] Statistically significant at $p < 0.05$.

Key finding: The authors found that maternal iodine status is predictive of neurodevelopmental outcomes in offspring. The relationship between fT4 at various periods of gestation was consistently associated with verbal, performance, and FSIQ, but failed to reach statistical significance.

Cognitive (Bayley Scales)

Detailed Summary of Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>1999</Year><RecNum>40</RecNum><DisplayText>(1999)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062208">40</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Kuijpens, J L</author><author>van Baar, A L</author><author>Verkerk, G</author><author>van Son, M M</author><author>de Vijlder, J J</author><author>Vulsma, T</author><author>Wiersinga, W M</author><author>Drexhage, H A</author><author>Vader, H L</author></authors></contributors><titles><title>Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>149-155</pages><volume>50</volume><section>149</section><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>]

Low Maternal Free Thyroxine Concentrations During Early Pregnancy Are Associated with Impaired Psychomotor Development in Infancy

Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>1999</Year><RecNum>40</RecNum><DisplayText>(1999)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062208">40</key></foreign-

keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Kuijpens, J L</author><author>van Baar, A L</author><author>Verkerk, G</author><author>van Son, M M</author><author>de Vijlder, J J</author><author>Vulsma, T</author><author>Wiersinga, W M</author><author>Drexhage, H A</author><author>Vader, H L</author></authors></contributors><titles><title>Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>149-155</pages><volume>50</volume><section>149</section><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>] conducted a prospective cohort study to examine the association between maternal thyroid hormones during early gestation and children's neurodevelopment in an iodine-sufficient region. Women were recruited from a medical center and from community midwife practices at 12 GW. In the 291 healthy women who consented to participate, assessments of maternal thyroid function—fT4, TSH, and TPO Ab levels—were completed at 12 GW and 32 GW. At various stages of follow-up, women were excluded from the study due to neonatal deaths, moving outside of the area, and other pregnancy complications. Children of women remaining in the study at 10 months post-partum (n = 220) completed the Dutch version of the Bayley Scales of Infant Development (BSID) to evaluate mental and psychomotor development using the MDI and PDI, respectively. Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>1999</Year><RecNum>40</RecNum><DisplayText>(1999)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062208">40</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Kuijpens, J L</author><author>van Baar, A L</author><author>Verkerk, G</author><author>van Son, M M</author><author>de Vijlder, J J</author><author>Vulsma, T</author><author>Wiersinga, W M</author><author>Drexhage, H A</author><author>Vader, H L</author></authors></contributors><titles><title>Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>149-155</pages><volume>50</volume><section>149</section><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>] conducted t-tests to investigate maternal thyroid levels in the lowest 5th (< 9.8 pmol/L) and 10th (< 10.4 pmol/L) percentiles of fT4 levels at 12 and 32 GW. The authors also performed linear and logistic regression analyses, adjusted for confounders including maternal depression, psychosocial factors, tobacco and alcohol use during pregnancy, and demographic variables. Data analyses were conducted using t-tests, linear regression, and logistic regression.

Children of the 22 women in the lowest 10th percentile of fT4 at 12 GW had significantly lower scores on the PDI than the rest of the children (mean difference: 7.4, 95% CI: 1.1, 13.9). No significant differences were found when investigating PDI scores at 32 GW. MDI scores showed differences associated with fT4 levels, but these failed to reach significance at both 12 and 32 GW. Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>1999</Year><RecNum>40</RecNum><DisplayText>(1999)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062208">40</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V

J</author><author>Kuijpens, J L</author><author>van Baar, A L</author><author>Verkerk, G</author><author>van Son, M M</author><author>de Vijlder, J J</author><author>Vulsma, T</author><author>Wiersinga, W M</author><author>Drexhage, H A</author><author>Vader, H L</author></authors></contributors><titles><title>Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>149-155</pages><volume>50</volume><section>149</section><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>] also found a strong correlation between PDI scores and maternal fT4 levels ($r = 0.46$, $p = 0.03$) (see [REF _Ref457471597 \h]). Although the authors did not present the equation representing the relationship in [REF _Ref457471597 \h],[12] their Figure 2 was digitized using the WebPlotDigitizer Extension for Google Chrome and using the linear regression function in Excel on the extracted data. By doing so it was determined that for every 1 pmol/L change in fT4 there is an estimated 8.5 point change in PDI (95% CI: 0.01 - 17.04).[13] Children of mothers with fT4 concentrations in the lowest fT4 5th percentile (n = 11) and 10th percentile also had lower scores on the MDI subscale, although these differences were not significant. The results suggest that the timing of hypothyroxinemia during pregnancy may be important as it relates to performance on the BSID.

Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>1999</Year><RecNum>40</RecNum><DisplayText>(1999)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062208">40</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Kuijpens, J L</author><author>van Baar, A L</author><author>Verkerk, G</author><author>van Son, M M</author><author>de Vijlder, J J</author><author>Vulsma, T</author><author>Wiersinga, W M</author><author>Drexhage, H A</author><author>Vader, H L</author></authors></contributors><titles><title>Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in

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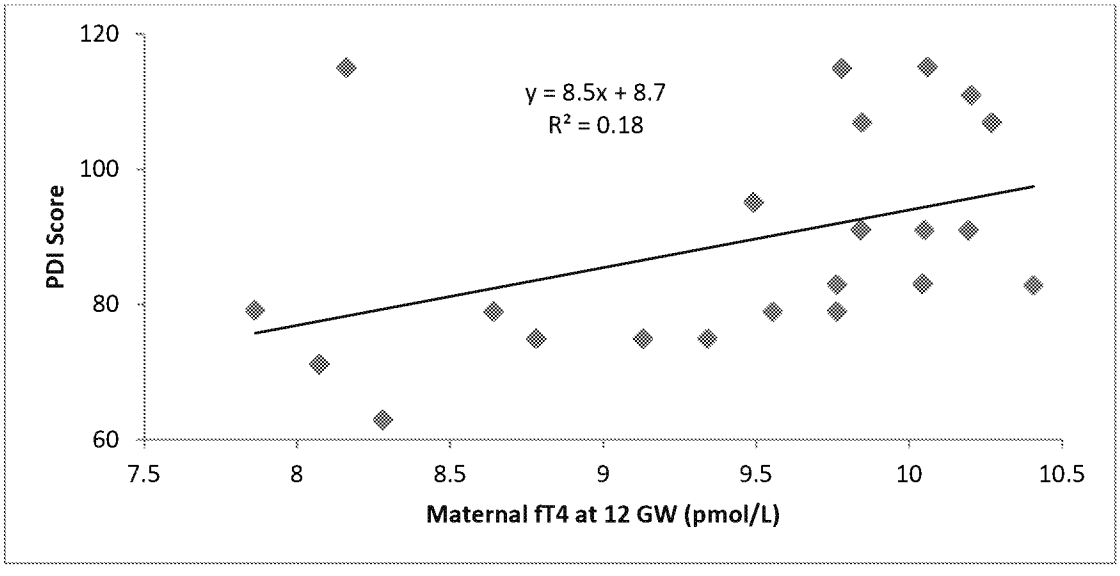
[12] The EPA attempted to contact study authors on July 20, 2015. To date, no response has been received.

[13] R^2 value based on Excel analysis = 0.18; R^2 value reported by Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>1999</Year><RecNum>40</RecNum><DisplayText>(1999)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062208">40</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Kuijpens, J L</author><author>van Baar, A L</author><author>Verkerk, G</author><author>van Son, M M</author><author>de Vijlder, J J</author><author>Vulsma, T</author><author>Wiersinga, W M</author><author>Drexhage, H A</author><author>Vader, H L</author></authors></contributors><titles><title>Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>149-155</pages><volume>50</volume><section>149</section><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>] = 0.21.

infancy</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>149-155</pages><volume>50</volume><section>149</section><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>] additionally performed logistic regression analyses to investigate associations between maternal variables and low PDI scores (defined as below 84 points). In univariate regression analyses, fT4 in the lowest 10th percentile at 12 GW was significantly associated with a low PDI score (relative risk (RR) = 3.6; 95% CI: 1.1-12.1). To control for the effect of possible confounders, Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>1999</Year><RecNum>40</RecNum><DisplayText>(1999)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062208">40</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Kuijpens, J L</author><author>van Baar, A L</author><author>Verkerk, G</author><author>van Son, M M</author><author>de Vijlder, J J</author><author>Vulsma, T</author><author>Wiersinga, W M</author><author>Drexhage, H A</author><author>Vader, H L</author></authors></contributors><titles><title>Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>149-155</pages><volume>50</volume><section>149</section><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>] performed a multiple logistic regression analysis that included a host of additional pregnancy-related factors, maternal mood indicators, and demographic features. The relative risk estimate for the association between fT4 in the lowest 10th percentile at 12 GW and low PDI scores increased (RR = 5.8; 95% CI: 1.3-12.6) in the multivariate regression analysis. No significant associations were found in univariate or multivariate regression analyses between fT4 in the lowest 10th percentile at 32 GW and low PDI scores.

Figure [SEQ Figure * ARABIC]. Digitization of Figure 2 from Pop et al. (1999): Correlation between PDI Score and fT4 at 12 GW for Women in the Lowest 10th Percentile of fT4



***Key finding*:** Maternal fT4 levels in the lowest 10th percentile in the first trimester among an iodine-sufficient population were significantly associated with reduced psychomotor development in 10-month-old infants (a drop in the PDI score of 8.5 points was associated with every 1 pmol/L reduction in fT4).

Detailed Summary of Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>]

Maternal Hypothyroxinemia during Early Pregnancy and Subsequent Child Development: A 3-Year Follow-Up Study

In a prospective 3-year study, Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] measured thyroid hormone levels (TSH and fT4) in randomly selected pregnant women at 12, 24, and 32 GW in the Netherlands. Pop et al. initially approached 1,361 women to join their cohort. Eight of these women were excluded due to the presence of hyper- or hypothyroidism. From the remaining 1,353 women, Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical

Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] recruited 135 hypothyroxinemic cases (fT4 levels in the lowest 10th percentile (< 12.4 pmol/L)) and matched them based on parity and gravidity with an equal number of controls (fT4 levels in the 50th-90th percentiles (15.6–19.1 pmol/L)). TSH, fT4, and TPO Ab were assessed at 12 GW. At various stages of follow-up, women were excluded from the cohort due to a variety of exclusion criteria such as subclinical thyroid dysfunction (high TSH, normal fT4), fertility problems, autoimmune diseases, obstetrical complications, major depressive episodes, and prolonged or repeated hospitalizations after birth. This resulted in 63 cases and 62 controls at the age of 1 year and 57 cases and 58 controls at the age of 2 years. (For complete details on inclusion and exclusion of women in the cohort, see Figure 1 of Pop et al., 2003).

Infant development was assessed at 1 and 2 years of age using the Dutch version of the BSID to evaluate MDI and PDI scores. The mean scores for cases and controls are presented in [REF _Ref457848210 \h]. This table demonstrates that statistically significant differences in MDI and PDI existed between the cases and controls at both 1 and 2 years of age.

Table [SEQ Table * ARABIC]. Differences on Bayley Mental (MDI) and Motor (PDI) Subscales Assessed at 1 and 2 Years[a]

	Cases[b]	Controls[c]	*p*-value	95% CI
One Year				
Mental, mean (SD)	95 (15)	105 (14)	0.004	4-16
Motor, mean (SD)	91 (15)	99 (14)	0.02	3-12
Two Years				
Mental, mean (SD)	98 (15)	106 (14)	0.02	4-12
Motor, mean (SD)	92 (16)	102 (16)	0.005	6-16

Source: Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><Suffix>`, Table 2</Suffix><DisplayText>(2003, Table 2)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>].

[a] Based on a two-tailed t-test.

[b] fT4 levels in the lowest 10th percentile (< 12.4 pmol/L).

[c] fT4 levels in the 50th-90th percentiles (15.6–19.1 pmol/L).

Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma,

T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] also evaluated the relationship between maternal fT4 levels at 12 GW with MDI and PDI at 2 years of age. They determined that there was a significant correlation between maternal fT4 levels at 12 GW and both MDI and PDI scores (MDI: $r = 0.48$, $p = 0.001$; PDI: $r = 0.38$, $p = 0.006$) (see [REF _Ref457849041 \h]) among the women with hypothyroxinemia. Although Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] did not present the equation representing the relationship in [REF _Ref457849041 \h], their Figure 3 was digitized using the WebPlotDigitizer Extension for Google Chrome and using the linear regression function in Excel on the extracted data.[14] By doing so, it was determined that for every 1 pmol/L change in fT4 there is an estimated 8.4 point change in PDI

[14] The EPA attempted to contact study authors on July 20, 2015. To date, no response has been received.

(95% CI: 4.0–12.8)[15] and 6.3 point change in MDI (95% CI: 1.92–10.62).[16] Analogous analyses were not presented for individuals assessed at 1 year of age or for controls.

In addition, Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] examined the pattern of maternal fT4 levels throughout pregnancy and the distribution of Bayley Scales scores in the cases and controls. The authors found that the lowest Bayley scores were associated with the offspring of first-trimester hypothyroxinemic women (cases) whose fT4 levels continued to decrease as pregnancy progressed. Other women who

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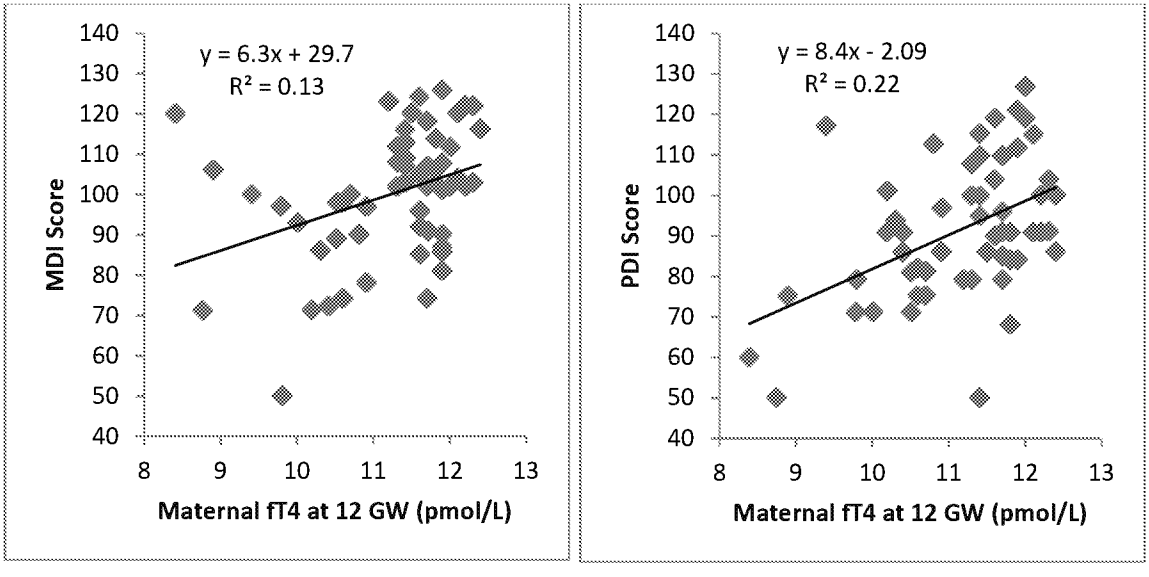
[15] R^2 value based on Excel analysis = 0.22; R^2 value reported by Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] = 0.23.

[16] R^2 value based on Excel analysis and reported by Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] = 0.13.

started out as hypothyroxinemic, but experienced increases in fT4 levels in either the second or third trimesters, had children with similar MDI and PDI scores to women who were not hypothyroxinemic in the first trimester. Additionally, the authors noted that children of women who had fT4 in the 50th to 90th percentile range during the first trimester (controls), but later experienced a drop in fT4, did not exhibit an association between neurodevelopment and fT4.

Figure [SEQ Figure * ARABIC]. Digitization of Figure 3 from Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>]: Linear Regression of Maternal fT4 Concentrations of Cases with fT4 in the Lowest 10th Percentile at 12 GW with MDI and PDI Scores at 2 Years of Age



Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma,

T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] note several potential shortcomings of their analysis. One is that the subgroups they assessed when evaluating the impact of the pattern of fT4 on PDI and MDI became very small because they excluded cases with potentially confounding data (e.g., mothers with episodes of depression). This may be why a statistical analysis of the individuals just in the group with low fT4 throughout pregnancy was not included in Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>]. Further, Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] noted that an assessment of a child's abilities at a very young age (i.e., less than 1 year of age) may have limited value once the child reaches school. However, Bayley scores at 2 years of age have been found capable of predicting a child's ability at 5 years, particularly if the child is at risk of developmental delays (Van Baar & De Graff, 1994, as cited in Pop et al., 2003; also see Appendix H). Additionally, no data on daily food or iodine intake in the population are available. The authors point out that previous studies in the same general population have reported sufficient iodine intake. However, according to the study authors, the sufficiency of this iodine intake specifically for pregnant women has been called into question (see van Rees-Wortelboer et al., 1987). Lastly, Pop et al. ([ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN"

db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] note that the trend in norms for the developmental tests are representative of the general population, since the mean MDI and PDI of controls in this study are similar to those reported in their prior 1999 study.

The Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] results indicate that hypothyroxinemia in the first trimester is associated with impaired mental and psychomotor development in childhood and that this relationship is likely to be even more pronounced in individuals with low fT4 throughout the entire course of pregnancy. Additionally, it should be noted that the relationship found between fT4 and PDI is essentially the same (i.e., for each pmol/L change in fT4 there is a resulting 8.4 point change in PDI) as that found by Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>1999</Year><RecNum>40</RecNum><DisplayText>(1999)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432062208">40</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Kuijpens, J L</author><author>van Baar, A L</author><author>Verkerk, G</author><author>van Son, M M</author><author>de Vijlder, J J</author><author>Vulsma, T</author><author>Wiersinga, W M</author><author>Drexhage, H A</author><author>Vader, H L</author></authors></contributors><titles><title>Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>149-155</pages><volume>50</volume><section>149</section><dates><year>1999</year></dates><urls></urls></record></Cite></EndNote>].

Key finding: Maternal fT4 levels in the lowest 10th percentile in the first trimester were significantly associated with a clinically relevant difference in psychomotor and mental development among

2-year-olds (a drop in the PDI score of 8.4 points and in the MDI score of 6.3 points was associated with every 1 pmol/L reduction in fT4).

Cognitive (Other)

Detailed Summary of Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>]

Maternal Hypothyroxinemia in Early Pregnancy Predicts Reduced Performance in Reaction Time Tests in 5- to 6-Year-Old Offspring

Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>] aimed to investigate the association between maternal fT4 and TSH concentrations and children's neurodevelopment, using a large, population-based cohort. Participants were recruited from pre-natal clinics in Amsterdam and excluded from the study if mothers used thyroid inhibitors during pregnancy or if children had congenital abnormalities. fT4 and TSH were measured once during pregnancy at a median gestational age of 12.9 weeks, and childhood cognitive performance was assessed 5 to 6 years later. TPO Ab positivity was also measured. The authors used the Amsterdam Neuropsychological Test (ANT) computerized assessment program, which consists of a series of tests to measure cognitive functioning such as reaction time and visuomotor coordination. Full biomarker and assessment data were available for 1,765 mother-child pairs. Since fT4 levels showed a slight negative association with gestational day, concentrations were standardized for the day of sampling. Linear regression models were constructed with adjustment for covariates including age, gender, demographic characteristics (e.g., birth order,

ethnicity), and pregnancy characteristic (e.g., BMI and diabetes). Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>] also compared children with and without hypothyroxinemia (< 10th percentile of fT4) and hyperthyrotropinemia (> 90th percentile of TSH) and examined interactions between the two. The authors additionally performed analyses after excluding subjects born pre-term (< 32 GW), with very low birthweight (< 1,500 g), or with test results ± 3 SD from the mean as a result of poor comprehension or motivation. TPO Ab-positive mothers were included in the main analysis, but a separate analysis found TPO Ab positivity was not related to any of the outcomes in [REF _Ref457841191 \h].

In all regression models tested, maternal fT4 levels were inversely associated with reaction time SD within an individual in a reaction time task. Maternal hypothyroxinemia was significantly associated with higher baseline reaction time when compared to non-hypothyroxinemic mothers (fT4 ≥ 10th percentile at the first pre-natal visit). Specifically, there was a 39.5 ms increase in mean reaction time and a 41.2 ms increase in SD of reaction time, when comparing the offspring of hypothyroxinemic to non-hypothyroxinemic mothers. Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>] also found an association between hypothyroxinemia (defined as fT4 < 10th or < 5th percentiles) and increased mean reaction time and reaction time SD. While mean reaction time is a general measure of speed, reaction time SD reflects the consistency of performance across time. The authors noted that the mean reaction time SD outcome "…has been found to be related more strongly to individual difference in intelligence, cognitive aging, and neurological disorders" than reaction time itself (Finken et al., 2013, p. 1419). While no associations between hyperthyrotropinemia and reaction test performance were observed, there was an interaction

between hypothyroxinemia and hyperthyrotropinemia; children of mothers with both conditions had a significantly greater reaction time mean and SD. Associations between maternal fT4 or TSH and other ANT outcomes (e.g., visuomotor coordination) were not observed. Results from the study are summarized in [REF _Ref457841191 \h]. Results remained similar in the additional analyses after excluding subjects.

Table [SEQ Table * ARABIC]. Summary of Results Evaluating the Relationship between Thyroid Hormones and Developmental Outcomes in Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>]

Test	Predictor	β (95% CI)	P
Baseline Speed			
Mean reaction time, milliseconds	fT4 (pmol/L)	-4.5 (-9.0; 0.1)	0.06
	TSH (mU/L)	2.3 (-1.3; 5.9)	0.21
Reaction time, SD, milliseconds	fT4 (pmol/L)	-4.9 (-9.5; -0.2)	0.04
	TSH (mU/L)	1.0 (2.7; 4.6)	0.61
Pursuit			
Deviation, millimeters	fT4 (pmol/L)	-0.01 (-0.22; 0.21)	0.95
	TSH (mU/L)	0 (-0.17; 0.17)	0.99
SD of deviation, millimeters	fT4 (pmol/L)	0 (-0.20; 0.21)	0.97
	TSH (mU/L)	0.04 (-0.12; 0.20)	0.65
Tracking			
Mean distance, millimeters	fT4 (pmol/L)	-0.01 (-0.11; 0.09)	0.78
	TSH (mU/L)	0.04 (-0.05; 0.11)	0.40
Accuracy stability, millimeters	fT4 (pmol/L)	0.04 (-0.06; 0.15)	0.42
	TSH (mU/L)	0.01 (-0.08; 0.09)	0.84
Movement speed, seconds	fT4 (pmol/L)	-0.08 (-0.34; 0.18)	0.55
	TSH (mU/L)	0.10 (-0.11; 0.31)	0.34
Response Organization Objects			
Part 1 (compatible)			
Mean reaction time, milliseconds	fT4 (pmol/L)	-5.1 (-12.1; 1.8)	0.15
	TSH (mU/L)	1.4 (-4.0; 7.0)	0.61
Reaction time, SD, milliseconds	fT4 (pmol/L)	-1.7 (-7.4; 3.9)	0.55
	TSH (mU/L)	4.6 (0.1; 9.1)	0.05
Part 2 (incompatible)			
Mean reaction time, milliseconds	fT4 (pmol/L)	2.0 (-7.6; 11.6)	0.69
	TSH (mU/L)	4.6 (-3.1; 12.3)	0.24
Reaction time, SD, milliseconds	fT4 (pmol/L)	0.9 (-6.7; 8.6)	0.82
	TSH (mU/L)	7.3 (1.2; 13.3)	0.02

Source: Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><Suffix>`, Table 3</Suffix><DisplayText>(2013, Table 3)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>].
Note: Results adjusted for gender and age at assessment, family background variables, including computer gaming (< 1 or ≥ 1 hr/day); birth order; maternal education (in 4 categories); ethnicity (Western or non-Western); and pregnancy characteristics, including maternal age, BMI, diabetes (yes or no), and hypertension (yes or no).

Key finding: Maternal fT4 levels at a median of 12.9 weeks were inversely associated with the reaction time variability among 5- to 6-year-old children (an increase in the reaction time SD of 4.9 ms was associated with every 1 pmol/L reduction in maternal fT4). Considering fT4 as a

categorical variable demonstrated that there was a 39.5 ms increase in mean reaction time and a 41.2 ms increase in SD of reaction time when comparing the offspring of hypothyroxinemic vs. non-hypothyroxinemic mothers.

Detailed Summary of Henrichs et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Henrichs</Author><Year>2010</Year><RecNum>16</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047636">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Henrichs, J</author><author>Bongers-Schokking, J J</author><author>Schenk, J J</author><author>Ghassabian, A</author><author>Schmidt, H G</author><author>Visser, T J</author><author>Hooijkaas, H</author><author>de Muinck Keizer-Schrama, S M P F</author><author>Hofman, A</author><author>Jaddo, V V W</author><author>Visser, W</author><author>Steegers, E A P</author><author>Verhulst, F C</author><author>de Rijke, Y B</author><author>Tiemeier, H</author></authors></contributors><titles><title>Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>4227-4234</pages><volume>95</volume><number>9</number><section>4227</section><dates><year>2010</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2010-0415</electronic-resource-num></record></Cite></EndNote>]

Maternal Thyroid Function during Early Pregnancy and Cognitive Functioning in Early Childhood: The Generation R Study

Henrichs et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Henrichs</Author><Year>2010</Year><RecNum>16</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047636">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Henrichs, J</author><author>Bongers-Schokking, J J</author><author>Schenk, J J</author><author>Ghassabian, A</author><author>Schmidt, H G</author><author>Visser, T J</author><author>Hooijkaas, H</author><author>de Muinck Keizer-Schrama, S M P F</author><author>Hofman, A</author><author>Jaddo, V V W</author><author>Visser, W</author><author>Steegers, E A P</author><author>Verhulst, F C</author><author>de Rijke, Y B</author><author>Tiemeier, H</author></authors></contributors><titles><title>Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>4227-4234</pages><volume>95</volume><number>9</number><section>4227</section><dates><year>2010</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2010-0415</electronic-resource-num></record></Cite></EndNote>] evaluated the relationship between early pregnancy TSH and fT4 levels in mothers and cognitive functioning of their children in a Netherlands-based study. Participants were recruited from a birth cohort and excluded if T4 treatment was received during pregnancy. Maternal blood was analyzed for fT4 and TSH at a mean GW of 13.3. TPO Abs

were not measured. Mothers were classified as having mild or severe hypothyroxinemia based on T4 levels < 10th (< 11.76 pmol/L) and < 5th percentiles (< 10.96 pmol/L), respectively. Parents completed several questionnaires to assess verbal development at age 18 months and verbal and nonverbal development at 30 months.

Verbal assessments at 18 and 30 months (the MacArthur Communicative Development Inventory and the Language Development Inventory, respectively) consisted of checklists of words; parents identified words spontaneously spoken by children, which were then summed to derive age- and gender-specific percentiles. Expressive language delay at age 18 or 30 months was operationalized as scores below the 15th percentile. Delay at 30 months was also indicated by a lack of word combinations (i.e., the child had not begun to construct phrases).

Nonverbal cognitive development was assessed using the Parent Report of Children's Abilities, which consists of questions to parents (e.g., on spatial ability, memory, and planning skills) and parent-administered tasks (e.g., building blocks). Cognitive delay was similarly defined as scores below the 15th age- and gender-specific percentiles. Logistic regression analyses were conducted with adjustment for maternal age, education, pre-natal distress, pre-natal smoking, birthweight, gestational age at blood sampling, and child ethnicity.

Results indicated that, while maternal TSH was not found to be related to the cognitive outcomes measured, maternal fT4 was found to be inversely related to expressive language delay at 30 months of age. Both mild and severe maternal hypothyroxinemia were found to be associated with a higher risk of expressive language delay across the age range of 18 months (OR = 1.44; 95% CI: 1.09, 1.91; $p = 0.010$) and 30 months of age (OR = 1.80; 95% CI: 1.24, 2.61; $p = 0.002$), respectively. Henrichs et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Henrichs</Author><Year>2010</Year><RecNum>16</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047636">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Henrichs, J</author><author>Bongers-Schokking, J J</author><author>Schenk, J J</author><author>Ghassabian, A</author><author>Schmidt, H G</author><author>Visser, T J</author><author>Hooijkaas, H</author><author>de Muinck Keizer-Schrama, S M P F</author><author>Hofman, A</author><author>Jaddo, V V W</author><author>Visser, W</author><author>Steegers, E A P</author><author>Verhulst, F C</author><author>de Rijke, Y B</author><author>Tiemeier, H</author></authors></contributors><titles><title>Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>4227-4234</pages><volume>95</volume><number>9</number><section>4227</section><dates><year>2010</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2010-0415</electronic-resource-num></record></Cite></EndNote>] also reported that severe hypothyroxinemia in the mothers was associated with a 2.03-fold increased risk of nonverbal cognitive delay in their children (95% CI: 1.22, 3.39, $p = 0.007$). The authors also found that fT4 levels per SD were associated with a higher risk of expressive language delay at 30 months (OR = 0.84, 95% CI: 0.71, 0.99). The SD specifically associated with this finding is not reported in Henrichs et al. [ADDIN EN.CITE <EndNote><Cite

ExcludeAuth="1"><Author>Henrichs</Author><Year>2010</Year><RecNum>16</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047636">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Henrichs, J</author><author>Bongers-Schokking, J J</author><author>Schenk, J J</author><author>Ghassabian, A</author><author>Schmidt, H G</author><author>Visser, T J</author><author>Hooijkaas, H</author><author>de Muinck Keizer-Schrama, S M P F</author><author>Hofman, A</author><author>Jaddo, V V W</author><author>Visser, W</author><author>Steegers, E A P</author><author>Verhulst, F C</author><author>de Rijke, Y B</author><author>Tiemeier, H</author></authors></contributors><titles><title>Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>4227-4234</pages><volume>95</volume><number>9</number><section>4227</section><dates><year>2010</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2010-0415</electronic-resource-num></record></Cite></EndNote>].[17] The findings of this study, summarized in [REF _Ref457844567 \h], indicate that children born to mothers with hypothyroxinemia are at an increased risk of cognitive delays in early childhood.

[17] Study authors were contacted on November 18, 2016, for this information and have not yet responded.

Table [SEQ Table * ARABIC]. Summary of Results from Henrichs et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Henrichs</Author><Year>2010</Year><RecNum>16</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047636">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Henrichs, J</author><author>Bongers-Schokking, J J</author><author>Schenk, J J</author><author>Ghassabian, A</author><author>Schmidt, H G</author><author>Visser, T J</author><author>Hooijkaas, H</author><author>de Muinck Keizer-Schrama, S M P F</author><author>Hofman, A</author><author>Jaddo, V V W</author><author>Visser, W</author><author>Steegers, E A P</author><author>Verhulst, F C</author><author>de Rijke, Y B</author><author>Tiemeier, H</author></authors></contributors><titles><title>Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>4227-4234</pages><volume>95</volume><number>9</number><section>4227</section><dates><year>2010</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2010-0415</electronic-resource-num></record></Cite></EndNote>]

Maternal Thyroid Function Measure	Expressive Language Delay at 18 Months		Expressive Language Delay at 30 Months		Expressive Language Delay at 18 and 30 Months		Nonverbal Cognitive Delay at 30 Months	
	n	OR (95% CI) *p*-value	n	OR (95% CI) *p*-value	n	OR (95% CI) *p*-value	n	OR (95% CI) *p*-value
TSH, per SD	3384	0.91 (0.81; 1.03) 0.136	2757	0.92 (0.81; 1.06) 0.249	3614	0.92 (0.84; 1.02) 0.100	2588	0.98 (0.88; 1.10) 0.759
fT4, per SD	3409	0.95 (0.83; 1.09) 0.430	2779	0.84 (0.71; 0.99) **0.039**	3643	0.90 (0.80; 1.01) 0.069	2606	0.85 (0.72; 1.01) 0.057
Mild hypothyroxi-nemia	2736	1.33 (0.91; 1.94) 0.143	2225	1.47 (1.00; 2.17) 0.051	2926	1.44 (1.09; 1.91) **0.010**	2086	1.37 (0.90; 2.07) 0.139
Severe hypothyroxi-nemia	2736	1.77 (1.10; 2.84) **0.018**	2225	1.78 (1.07; 2.94) **0.024**	2926	1.80 (1.24; 2.61) **0.002**	2086	2.03 (1.22; 3.39) **0.007**

Source: Henrichs et al. (2010, Tables 2 and 3).

Key Finding: Severe maternal hypothyroxinemia was associated with expressive language delay at 18 and 30 months and nonverbal cognitive delay at 30 months. Further, there was an increase in the

odds of expressive language delay and nonverbal cognitive delay when comparing the offspring of children exposed to mild versus severe maternal hypothyroxinemia, suggesting a potential dose-response between the severity of hypothyroxinemia and expressive language delay and nonverbal cognitive delay. Additionally, maternal fT4 levels per SD were associated with a reduction in odds of expressive language delay at 30 months (OR = 0.84 per SD of fT4).

Detailed Summary of Kasatkina et al. (2006)

Gestational Hypothyroxinemia and Cognitive Function in Offspring

Kasatkina et al. (2006) investigated the effect of maternal hypothyroxinemia on the cognitive function of offspring with maternal iodine deficiency. Maternal thyroid hormones (TSH, fT4) and TPO Ab were measured during the first trimester (5-9 GW) in 24 pregnant Russian women, and 13 of them were hypothyroxinemic. Hypothyroxinemia was defined as fT4 levels less than the 10th percentile. Children underwent neurological assessments at 6, 9, or 12 months of age using a standardized clinical-psychological method for evaluating neurological development called the Gnome method. From this, a calculation of the coefficient of mental development (CMD) was obtained for children up to 3 years of age. Normal neurological development was defined as CMD of 90-100 points; risk of delayed neuropsychological development was defined as CMD of 80-89 points; and delayed neurological development was identified as CMD of less than 80 points. Covariates, confounders, and any model adjustments were not displayed in the study. Fisher's, Student, and Mann-Whitney tests were used to compare relative values. Relationships between parameters were assessed by a Spearman correlation analysis.

Kasatkina et al. (2006) performed a Spearman correlation analysis of the relationship between maternal fT4 at 5-9 GW and CMD. The authors found a strong, direct association between the level of maternal fT4 in weeks 5–9 of pregnancy and CMD in children at age 6 months ($r = 0.684$, $p = 0.020$), 9 months ($r = 0.629$, $p = 0.038$), and 12 months ($r = 0.708$, $p = 0.014$). The authors also did a comparative analysis of CMD elements at 6, 9, and 12 months comparing children born to mothers with hypothyroxinemia (which was corrected with iodine treatment) to mothers with normal fT4 levels. The children born to mothers with corrected hypothyroxinemia had consistently lower scores for CMD, motor function, and cognitive function at 6, 9, and 12 months (with one exception that at 12 months cognitive function was slightly higher in the children born to mothers with corrected hypothyroxinemia). However, none of the differences were statistically significant results.

Key Finding: The authors found that maternal fT4 levels in early pregnancy correlated significantly with CMD in children at ages 6, 9, and 12 months. When comparing CMD scores with the offspring of mothers with corrected hypothyroxinemia to the offspring of mothers with normal fT4, consistently lower scores for CMD, motor function, and cognitive function at 6, 9, and 12 months were seen, though the difference did not reach statistical significance.

Detailed Summary of Noten et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA]

Maternal Hypothyroxinaemia in Early Pregnancy and School Performance in 5-Year-Old Offspring

Noten et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] examined the effect of hypothyroxinemia during pregnancy on school performance of offspring at 5 years of age. In line with other studies, hypothyroxinemia was defined as an fT4 level less than the 10th percentile of distribution (< 8.06 pmol/L in their sample). Participants were recruited from the Amsterdam Born Children and Their Development study. After exclusion criteria that included mothers who were lost

to follow-up or who did not give consent for their child's school test results, 1,196 mother-child pairs were included in the study population. Maternal fT4, TSH, and TPO Ab (> 80 kU/L was considered positive) were measured around the beginning of the second trimester (mean gestational age of 12.9 weeks, interquartile range 11.9-14.3 weeks).

School records of offspring were based on scores obtained in arithmetic and language tests from the Central Institute for Test Development, a national monitoring and evaluation system in the Netherlands. Multivariable logistic regression was used to assess the effects of fT4 and TSH on the range of poor or subnormal school performance (defined as a rank score below C or B, respectively). Models were adjusted for maternal education, ethnicity, BMI, and depressive symptomatology, as these were related to both the exposure to maternal hypothyroxinemia and outcome of school performance ($p < 0.1$). Maternal age, hypertension, diabetes, smoking, timing of blood sampling, TPO Ab positivity, child gender, gestational age, and birthweight were evaluated as potential confounders, but were found to not be associated with the predictor and outcome and thus not included in the regression analyses. Additional analyses were repeated after excluding pre-term births (< 32 weeks of gestation) or very low birthweight offspring (< 1,500 grams).

The distribution of school test results in terms of rank scores differed between hypothyroxinemic and non-hypothyroxinemic groups, with hypothyroxinemia being associated with lower rank scores in both arithmetic and language tests. Maternal hypothyroxinemia was significantly associated with 1.61-fold (95% CI: 1.05-2.47; $p = 0.03$) increased odds of subnormal arithmetic school performance after adjusting for confounders. However, this association weakened, reaching non-significance, after inverse-probability weighting was applied to account for potential non-response bias. No associations were found with TSH, even before inverse probability weighting. The continuous measure maternal fT4 was inversely associated with the odds of subnormal arithmetic performance, but lost statistical significance after adjusting for confounders. Additional exclusion of pre-term births or very low birthweight offspring did not change these associations.

Key finding: Maternal hypothyroxinemia at the end of the first trimester was associated with reduced arithmetic test performance in 5-year-old offspring. Inverse probability weighting demonstrates that non-response bias may be present in this study, and thus the results should be interpreted with caution.

Detailed Summary of Oken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Year>2009</Year><RecNum>22</RecNum><DisplayText>(2009)</DisplayText><record><rec-number>22</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047640">22</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oken, E</author><author>Braverman, L</author><author>Platek, D</author><author>Mitchell, M L</author><author>Lee, S L</author><author>Pearce, E N</author></authors></contributors><titles><title>Neonatal thyroxine, maternal thyroid function, and child cognition</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>497-503</pages><volume>94</volume><number>2</number><section>497</section><dates><year>2009</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2008-0936</electronic-resource-num></record></Cite></EndNote>]

Neonatal Thyroxine, Maternal Thyroid Function, and Child Cognition

Oken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Year>2009</Year><RecNum>22</RecNum><DisplayText>(2009)</DisplayText><record><rec-number>22</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047640">22</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oken, E</author><author>Braverman, L</author><author>Platek, D</author><author>Mitchell, M L</author><author>Lee, S L</author><author>Pearce, E N</author></authors></contributors><titles><title>Neonatal thyroxine, maternal thyroid function, and child cognition</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>497-503</pages><volume>94</volume><number>2</number><section>497</section><dates><year>2009</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2008-0936</electronic-resource-num></record></Cite></EndNote>] examined the relationship between maternal thyroid levels, neonatal thyroid levels, and neurodevelopmental outcomes in childhood. Participants were recruited from a birth cohort and were included in the study if complete information was available on their diet, infant cognition, and T4 levels; women with a history of thyroid problems, pregnancy complications, or other health issues were not excluded from the study. Maternal TSH, total T4, and TPO Ab levels were assayed once during the first trimester (mean 10.2 GW). The researchers did not measure fT4. Neonatal total T4 levels were sampled around 2 days after birth. Children underwent neurodevelopmental testing at 6 months and 3 years. At 6 months, children completed the Visual Recognition Memory (VRM) test, which measures the ability of an infant to recognize visual stimuli and to respond preferentially to novel stimuli. The Peabody Picture Vocabulary Test (PPVT) and the Wide Range Assessment of Visual Motor Ability (WRAVMA) were administered at 6 years of age. The VRM and PPVT have been found to be good predictors of later intelligence, with levels of predictive validity similar to those of the BSID [ADDIN EN.CITE <EndNote><Cite><Author>Oken</Author><Year>2009</Year><RecNum>22</RecNum><DisplayText>(Oken et al., 2009)</DisplayText><record><rec-number>22</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047640">22</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Oken, E</author><author>Braverman, L</author><author>Platek, D</author><author>Mitchell, M L</author><author>Lee, S L</author><author>Pearce, E N</author></authors></contributors><titles><title>Neonatal thyroxine, maternal thyroid function, and child cognition</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>497-503</pages><volume>94</volume><number>2</number><section>497</section><dates><year>2009</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2008-0936</electronic-resource-num></record></Cite></EndNote>]. The WRAVMA assesses visual-spatial analysis, visual-motor ability, and fine motor skills. Linear regression models, adjusted for other variables such as gender and age at delivery, were used to investigate the relationship between thyroid hormone levels and neurodevelopmental outcomes, with adjustment for covariates including gestation length, age at testing, sex, maternal education, and ethnicity.

Neonatal total T4 was not associated with either the PPVT or WRAVMA scores. Contrary to expectations, it was associated with lower scores on the VRM test, both as a continuous variable (β = -0.5; 95% CI -0.9, -0.2) and as a categorical variable. Maternal thyroid function (as assessed by total T4, TSH, TPO Ab, and history of thyroid disease) was not associated with children's scores on any of the neurodevelopmental outcomes studied. Further, maternal and neonatal total T4 were evaluated, as opposed to fT4, which is the form of the hormone that is available to cross the placenta and may be a better indicator for an offspring's neurodevelopmental outcome. There was no significant association between maternal total T4 levels and neonatal total T4 levels.

Key Finding: Neonatal total T4 levels within the euthyroid range were not predictive of cognitive outcome, nor were they associated with maternal T4 levels. Maternal thyroid function (T4, TSH, and TPO Ab measured at approximately 10 GW) was not associated with any of the neurodevelopmental outcomes assessed. This study did not make an attempt to separately analyze hypothyroxinemic maternal-child pairs.

Behavior

Detailed Summary of Endendijk et al. (2017)

Maternal Thyroid Hormone Trajectories during Pregnancy and Child Behavioral Problems

Endendijk et al. (2017) examined associations between maternal thyroid hormone trajectories and child behavior problems based on thyroid assessments at separate trimesters of pregnancy. The authors assessed 442 pregnant Dutch mothers at 12, 24, and 36 GW for thyroid hormone levels (TSH and fT4) and TPO Abs in blood serum. Mothers and fathers reported on their child's behavior problems between 23 and 60 months of age by individually completing the Child Behavior Check List (CBCL) (for more information on the CBCL, please refer to Appendix H). The version of the CBCL the authors used was developed for children between 1.5 and 5 years old and contains 100 behavioral and emotional problem items. For each item, parents indicated if a problem was seen frequently or not. The results were differentiated into internalizing (anxiety, depression, withdrawn behavior) or externalizing (attention difficulties, aggression) problems. Potential covariates considered for this analysis included gestational age and weight at birth, child age at time of CBCL assessment, parity, breastfeeding, mothers' age, maternal psychopathology symptoms (pre-natal and at time of CBCL assessment), smoking and alcohol use during pregnancy, educational level, and TPO

Ab positivity. Analysis of variance (ANOVA) or chi-squared tests were used to compare the different thyroid trajectory groups with regard to the covariates, and internalizing and externalizing problems.

Endendijk et al. (2017) reported a significant effect of first-trimester fT4 on anxiety/depression ($\beta = -0.12$, $p < 0.05$).[18] The authors also found that maternal thyroid hormones over the course of pregnancy predicted child anxiety/depression better than first-trimester fT4 levels alone. Further, the authors looked for differences in sex with correlations between maternal thyroid hormones and internalizing and externalizing problems. Lower fT4 in the first trimester was associated with more internalizing problems with girls only, primarily driven by anxiety/depression ($r = 0.17$, $p < 0.05$). However, between girls and boys, the association between first-trimester fT4 and anxiety/depression was not statistically different.

Key finding: The authors reported a significant effect of first-trimester fT4 on anxiety/depression. They did not do an analysis specific to the hypothyroxinemic population. The authors also found that maternal thyroid hormones over the course of pregnancy predicted child anxiety/depression better than first-trimester fT4 levels alone.

Detailed Summary of Ghassabian et al. (2011)

Maternal Thyroid Function during Pregnancy and Behavioral Problems in the Offspring: the Generation R Study

Ghassabian et al. (2011) evaluated the association of maternal thyroid function with parent-reported problem behavior in offspring up to 3 years old. Maternal thyroid function data, including TSH and fT4, were assessed at the first pre-natal visit (mean = 13.3 GW, SD = 1.7). Child behavior, or the degree of internalizing (anxiety, sadness, and withdrawn behavior) and externalizing (attention problems and aggressive behavior) problems, was assessed with the CBCL at ages 1.5 and 3 years of age. The CBCL contains a standardized rating of behavioral and emotional problems based on 99 items that, in this study, was completed by both mothers and fathers. Pregnant mothers were recruited from the Generation R cohort, a population-based cohort in Rotterdam, Netherlands. The main exclusion criteria was if women were using thyroid medication. In total, 3,736 children of mothers with maternal thyroid hormone data and behavioral data (from either mothers' or fathers' responses to the CBCL) were included in the study. CBCL scores were analyzed as continuous dependent variables. Multiple linear regression analysis was used to assess maternal thyroid hormone function associations with their child's internalizing and externalizing scores at 1.5 and 3 years of age. Confounders included in the final model were maternal age, educational level and psychopathology, child's gender and ethnicity, mode of delivery, and gestational age at the time of thyroid sampling.

Maternal hypothyroxinemia was mildly associated with higher internalizing scores of children at 1.5 and 3 years of age ($\beta = -0.19$ for hypothyroxinemic mothers; 95% CI, -0.75 and 0.37; $p = 0.51$). In addition, there was no association between maternal hypothyroxinemia and externalizing scores ($\beta = 0.17$ for hypothyroxinemic mothers; 95% CI, -0.53 and 0.87; $p = 0.64$). There was also no association between maternal fT4 and TT4 with the children's externalizing scores at 1.5 and 3 years of age.

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[18] Personal communication with study authors revealed that anxiety/depression scores were inverse transformed.

Key finding: The authors did not find maternal fT4 to be associated with internalizing or externalizing scores of children. Maternal hypothyroxinemia was mildly associated (though not statistically significant) with higher internalizing or externalizing scores of children at 1.5 and 3 years of age.

Detailed Summary of Modesto et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA]

Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children

Modesto et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] examined the relationship between exposure to maternal mild thyroid hormone insufficiency in early pregnancy and ADHD in offspring at 8 years of age. Maternal thyroid function data, including TSH, fT4, and TPO Abs, were assessed during the first or second trimester at a mean of 13.6 (range 6.6–17.9) weeks of gestation. Mothers using the Conners' Parent Rating Scale-Revised Short Form assessed children's ADHD at 8 years of age. This assessment includes the four scales: Cognitive Problems/Inattention, Hyperactivity, Oppositional, and the ADHD index (ADHDi). The possible range of scores for this test is 0–36 with higher scores indicating more ADHD symptoms. Maternal hypothyroxinemia was defined as TSH levels within the population reference range (0.1 to 2.5 mIU/L) and low fT4 levels below the 5th percentile of the sample (< 0.85 ng/dL = 10.94 pmol/L). Positive results for TPO Abs were defined as plasma concentrations of 100 IU/mL or greater. Pregnant mothers were recruited if they lived in the municipality of Rotterdam, Netherlands, and were in the Generation R Study. The main exclusion criteria for mother-child pairs were birth of twins, availability of thyroid hormone data, and if no return assessment occurred of child with mother (or caregiver) by 6 years of age of the child.

Continuous measures of TSH and fT4 were divided by their standard deviations to easily compare their associations with outcomes ([REF _Ref475433275 \h * MERGEFORMAT]). The authors examined associations between maternal thyroid function (across the entire range of fT4, not just the hypothyroxinemic range) with a child's ADHDi and Oppositional scores using linear regression. To satisfy the assumption of normality, these scores were transformed using natural logarithms. Regression coefficients were subsequently exponentiated and converted to percentage differences. Models were adjusted for the possible confounders of child age, sex, ethnic background, and parity, and maternal education level, smoking history, psychopathologic symptoms in pregnancy, age, marital status, household income, BMI, and gestational age at the time of blood sampling for maternal thyroid function data. Models were additionally adjusted for the following potential confounders in separate steps to test specificity of the findings: child's autistic symptoms, nonverbal IQ, Oppositional scores, or ADHDi scores.

In general, children of mothers with maternal hypothyroxinemia (127 mothers) in early pregnancy had higher ADHDi scores at 8 years old when compared to children without exposure to maternal hypothyroxinemia, after adjusting for the factors described above (7% increase in ADHDi scores (95% CI: 0.3%-15%)). Additional adjustments for a child's autistic symptoms or Oppositional scores did not affect this association. The results remained mostly unchanged when women with elevated TPO Abs were excluded. A separate analysis focusing on a fetal gestational age of less than 13 weeks at the time of sampling found statistically significant associations, after adjusting for age and sex, between maternal hypothyroxinemia and ADHDi scores ($\beta = 0.15$; 95% CI: 0.01, 0.28; $p = 0.04$) and between fT4 and ADHDi scores ($\beta = -0.02$; 95% CI: -0.04, -0.001; $p = 0.04$) at 8 years of age. However, when fully adjusted (for child age, sex, ethnic background, maternal educational level, age,

history of smoking, psychopathologic symptoms during pregnancy, parity, marital status, household income, BMI, and time of blood sampling in pregnancy), the relationship between fT4 and ADHDi scores was no longer statistically significant (β = -0.02; 95% CI: -0.03, 0.003; p = 0.10). No associations were found between maternal subclinical hypothyroidism and ADHDi score in children; and maternal thyroid function in early pregnancy and children's Oppositional scores at 8 years of age.

Table [SEQ Table * ARABIC]. Summary of Results[a] Evaluating the Relationship Between Maternal Thyroid Function in Early Pregnancy and Children's ADHDi Scores at 8 Years of Age

Thyroid Function Variable	Parent-Reported ADHDi Score: β (95% CI)	Changes in Scores, % (95% CI)
Maternal Hypothyroxinemia[b]		
Unadjusted	0.08 (0.01, 0.15)[d]	8 (1, 16)
Adjusted for age and sex	0.08 (0.01, 0.15)[d]	8 (1, 16)
Fully adjusted model[c]	0.07 (0.003, 0.14)[d]	7 (3, 15)
Free T4 Level per Standard Deviation[e]		
Unadjusted	-0.01 (-0.02, 0.01)	-1 (-2, 1)
Adjusted for age and sex	-0.01 (-0.02, 0.01)	-1 (-2, 1)
Fully adjusted model[c]	-0.01 (-0.02, 0.01)	-1 (-2, 1)
TSH Level per Standard Deviation[f]		
Unadjusted	-0.01 (-0.02, 0.01)	-1 (-2, 1)
Adjusted for age and sex	-0.01 (-0.02, 0.003)	-1 (-2, 0.3)
Fully adjusted model[c]	-0.01 (-0.02, 0.01)	-1 (-2, 1)
Maternal Hypothyroxinemia (TSH cut point 0.03-4.04 mIU/L)[b]		
Unadjusted	0.05 (-0.01, 0.11)	5 (-1, 12)
Adjusted for age and sex	0.05 (-0.01, 0.11)	5 (-1, 12)
Fully adjusted model[c]	0.05 (-0.01, 0.11)	5 (-1, 12)
Maternal Hypothyroxinemia (gestational age < 13 weeks at time of sampling)[b]		
Unadjusted	0.17 (0.03, 0.31)[d]	18 (3, 36)
Adjusted for age and sex	0.15 (0.01, 0.28)[d]	16 (1, 32)
Fully adjusted model[c]	0.13 (-0.01, 0.26)	14 (-1, 29)
Free T4 Level per Standard Deviation (gestational age < 13 weeks at time of sampling)[e]		
Unadjusted	-0.02 (-0.04, -0.004)[d]	-2 (-4, -0.4)
Adjusted for age and sex	-0.02 (-0.04, -0.001)[d]	-2 (-4, -0.1)
Fully adjusted model[c]	-0.02 (-0.03, 0.003)	-2 (-3, 0.3)
TSH Level per Standard Deviation (gestational age < 13 weeks at time of sampling)[f]		
Unadjusted	-0.004 (-0.02, 0.01)	-0.4 (-2, 1)
Adjusted for age and sex	-0.01 (-0.02, 0.01)	-1 (-2, 1)
Fully adjusted model[c]	-0.004 (-0.02, 0.01)	-0.4 (-2, 1)

Source: Modesto et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA].

[a] Results are presented in ng/dL unless otherwise noted.

[b] Categorical analysis.

[c] Adjusted for child age, sex, ethnic background, maternal educational level, age, history of smoking, psychopathologic symptoms during pregnancy, parity, marital status, household income, BMI, and time of blood sampling in pregnancy.

[d] Statistically significant at $p < 0.05$.

[e] The SD for fT4 is 0.29 ng/dL.

[f] The SD for TSH is 1.3 mIU/L.

Key finding: Maternal hypothyroxinemia in early pregnancy was associated with higher ADHDi scores in 8-year-old children compared with non-exposed children, after adjusting for confounders (7% increase in ADHDi scores (95% CI: 3%-15%)). When considering fT4 as a continuous variable, the association between maternal fT4 and offspring ADHDi scores was attenuated with the adjustment of confounders.

Detailed Summary of Oostenbroek et al. (2017)

Maternal Hypothyroxinaemia in Early Pregnancy and Problem Behavior in 5-Year-Old Offspring

Oostenbroek et al. (2017) investigated the association between maternal thyroid hormone function in early pregnancy and several types of problem behavior in offspring at age 5-6 years. The authors conducted a longitudinal study that used data from 2,000 mother-child pairs from the Amsterdam Born Children and their Development study. Primary exclusion criteria included children with congenital malformations and children of women who used anti-thyroid drugs during pregnancy. The median gestational age at maternal blood thyroid hormone (fT4 and TSH) measurement was 12.9 weeks (interquartile range: 11.9–14.1). Maternal hypothyroxinemia was defined at the cut points of fT4 level < 5th percentile (<7.75 pmol/L) and fT4 level < 10th percentile (<8.15 pmol/L).

Overall problem behavior, hyperactivity/ inattention, conduct problems, emotional problems, peer relationship problems, and prosocial behavior were measured at age 5–6 years using the Strengths and Difficulties Questionnaire (SDQ), which was filled out by both parents and teachers. The SDQ is a brief, validated questionnaire that can be filled out by the child's parents, caregivers, and/or teachers and is suitable for 3- to 16-year-old children. The questionnaire consists of 25 items subdivided into scales of hyperactivity/inattention, emotional problems, conduct problems, peer relationship problems, and prosocial behavior. Associations of continuous fT4 and TSH across the entire range of SDQ were assessed via multivariate logistic regression analysis. The adjusted model included ethnicity, years of education, pre-pregnancy BMI, hypertension, smoking during pregnancy of at least one cigarette per day, and anxiety level. Analyses were repeated after exclusion of children who were born very pre-term (i.e., <32 weeks) and/or with a very low birth weight (i.e., <1,500 g) and also after exclusion of children whose mothers were TPO Ab positive or on thyroid hormone supplements at their first visit.

[REF _Ref507166644 \h] summarizes the associations between maternal thyroid hormone function parameters and parent or teacher report of SDQ as assessed by Oostenbroek et al. (2017). None of the results presented reached statistical significance at $p < 0.05$. The authors also analyzed the same outcomes listed in [REF _Ref507166644 \h] with hypothyroxinemia at the <5th percentile and <10th percentile cut points. Significant results were seen for teacher reported hyperactivity/inattention in both the crude and adjusted model for the <5th percentile cut point (crude model: OR = 1.97, 95% CI: 1.19, 3.33, $p = 0.008$; adjusted model: OR = 1.70, 95% CI: 1.01, 2.86, p = 0.04) and in the crude model for the <10th percentile cut point (OR = 1.68, 95% CI: 1.15, 2.47; $p = 0.008$). Additionally, there was an association of borderline significance found between decreasing maternal fT4 and increased teacher-reported problem behavior.

Table [SEQ Table * ARABIC]. Associations between Maternal Thyroid Function Parameters and Parent or Teacher Report of SDQ

Outcomes (fT4, Continuous, pmol/L)	Crude Model OR (95% CI)	Adjusted Model OR (95% CI)[a]
Total Problems		
Parent reported	1.05 (0.91, 1.22)	1.10 (0.96, 1.27)
Teacher reported	0.85 (0.76, 0.96)	0.89 (0.79, 1.00)
Hyperactivity/Inattention		
Parent reported	0.97 (0.86, 1.09)	1.01 (0.90, 1.13)
Teacher reported	0.91 (0.82, 1.01)	0.95 (0.85, 1.05)
Emotional Problems		
Parent reported	1.03 (0.90, 1.18)	1.07 (0.93, 1.22)
Teacher reported	0.96 (0.83, 1.12)	0.95 (0.82, 1.12)
Conduct Problems		
Parent reported	0.92 (0.82, 1.03)	0.94 (0.84, 1.05)
Teacher reported	1.2[b] (0.92, 1.13)	1.04 (0.94, 1.15)
Peer Relationship Problems		
Parent reported	0.99 (0.89, 1.10)	1.02 (0.92, 1.14)
Teacher reported	1.04 (0.93, 1.18)	1.07 (0.95, 1.20)
Prosocial Problem Behavior		
Parent reported	1.02 (0.93, 1.13)	1.03 (0.93, 1.14)
Teacher reported	1.02 (0.94, 1.11)	1.03 (0.95, 1.12)

Source: Adapted from Oostenbroek et al. (2017, Tables 3 and 4).
[a] The Adjusted Model was adjusted for ethnicity, years of education, pre-pregnancy BMI, hypertension, smoking during pregnancy of at least 1 cigarette per day, and anxiety level.
[b] Result reported as "10.2" but this is assumed to be an error based on the 95% CI reported and other SDQ results presented.

***Key finding*:** An association of borderline significance was found between decreasing maternal fT4 and increasing teacher-reported problem behavior. Significant odds of increased hyperactivity/ inattention were seen in children of hypothyroxinemic mothers compared to mothers without hypothyroxinemia.

Autism

Detailed Summary of Román et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Román</Author><Year>2013</Year><RecNum>26</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047642">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Román, G C</author><author>Ghassabian, A</author><author>Bongers-Schokking, J</author><author>Jaddoe, V W V</author><author>Hofman, A </author><author>de Rijke, Y B</author><author>Verhulst, F C</author><author>Tiemeier, H</author></authors></contributors><titles><title>Association of gestational maternal hypothyroxinemia and increased autism risk</title><secondary-title>Annals of Neurology</secondary-title></titles><periodical><full-title>Annals of Neurology</full-title></periodical><pages>733-742</pages><volume>74</volume><number>5</number><section>733</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1002/ana.23976</electronic-resource-num></record></Cite></EndNote>]

Association of Gestational Maternal Hypothyroxinemia and Increased Autism Risk

Román et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Román</Author><Year>2013</Year><RecNum>26</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047642">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Román, G C</author><author>Ghassabian, A</author><author>Bongers-Schokking, J</author><author>Jaddoe, V W V</author><author>Hofman, A </author><author>de Rijke, Y B</author><author>Verhulst, F C</author><author>Tiemeier, H</author></authors></contributors><titles><title>Association of gestational maternal hypothyroxinemia and increased autism risk</title><secondary-title>Annals of Neurology</secondary-title></titles><periodical><full-title>Annals of Neurology</full-title></periodical><pages>733-742</pages><volume>74</volume><number>5</number><section>733</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1002/ana.23976</electronic-resource-num></record></Cite></EndNote>] conducted a study to examine the role of maternal hypothyroxinemia in autistic symptoms in children at 6 years of age. Participants were recruited from a population-based cohort in the Netherlands and included in the study complete biomarker and assessment data. Maternal TSH, fT4, and TPO Ab were measured near the beginning of the second trimester at a mean of 13.4 GW. Autistic symptoms were assessed via two questionnaires administered to parents: the Pervasive Developmental Problems Scale (PDP) and the Social Responsiveness Scale (SRS). The PDP is a subscale of the Child Behavior Checklist for Toddlers, which is an assessment of problem behaviors in children that is typically completed by parents or caregivers. The PDP measures autistic symptoms and has good predictive validity for identifying preschoolers at risk of ASD. The SRS is based on parent observations of social, language, and repetitive behaviors in a natural setting. Román et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Román</Author><Year>2013</Year><RecNum>26</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"

timestamp="1432047642">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Román, G C</author><author>Ghassabian, A</author><author>Bongers-Schokking, J</author><author>Jaddoe, V W V</author><author>Hofman, A </author><author>de Rijke, Y B</author><author>Verhulst, F C</author><author>Tiemeier, H</author></authors></contributors><titles><title>Association of gestational maternal hypothyroxinemia and increased autism risk</title><secondary-title>Annals of Neurology</secondary-title></titles><periodical><full-title>Annals of Neurology</full-title></periodical><pages>733-742</pages><volume>74</volume><number>5</number><section>733</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1002/ana.23976</electronic-resource-num></record></Cite></EndNote>] analyzed associations between maternal TSH and fT4 levels and PDP and SRS variables using linear and logistic regression models. Maternal fT4 levels were analyzed as a continuous variable (divided by the SD to facilitate interpretation) and categorically using definitions of mild and severe hypothyroxinemia (< 10^{th} and 5^{th} percentile of the sample, respectively). Children with borderline and clinical behavioral problems were defined as those above the 93^{rd} and 98^{th} percentiles on the PDP, respectively. A probable autistic child was defined by a PDP score > 98^{th} percentile and an SRS score in the top 5% of the sample. Regression models were adjusted for confounders including sex, ethnicity, gestation age, birthweight, parental age, education, smoking history, and intelligence. In the linear regression analysis PDP and SRS scores were square root-transformed to satisfy the normality assumption.

Román et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Román</Author><Year>2013</Year><RecNum>26</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047642">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Román, G C</author><author>Ghassabian, A</author><author>Bongers-Schokking, J</author><author>Jaddoe, V W V</author><author>Hofman, A </author><author>de Rijke, Y B</author><author>Verhulst, F C</author><author>Tiemeier, H</author></authors></contributors><titles><title>Association of gestational maternal hypothyroxinemia and increased autism risk</title><secondary-title>Annals of Neurology</secondary-title></titles><periodical><full-title>Annals of Neurology</full-title></periodical><pages>733-742</pages><volume>74</volume><number>5</number><section>733</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1002/ana.23976</electronic-resource-num></record></Cite></EndNote>] found no associations between the continuous measures of maternal TSH and fT4 per SD and children's borderline or clinical behavioral problems. However, the authors found that severe maternal hypothyroxinemia was associated with almost four-fold increased odds of having a probable autistic child (OR_{adj} = 3.89, 95% CI = 1.83, 8.20). Based on linear regression analysis, severe maternal hypothyroxinemia was also associated with a higher score of child autistic symptoms based on the PDP (β = 0.23, 95% CI = 0.07, 0.37) and SRS (β = 0.05, 95% CI = 0.01, 0.10) scales. However, the authors did not find this relationship to be concentration dependent. This is demonstrated by the negative associations seen between fT4 per SD and only mild hypothyroxinemia and the outcomes of lower PDP and SRS scale scores, as shown in [REF _Ref457851152 \h]. It is unknown if there is a concentration-dependent relationship between fT4 and scores on the PDP or SRS scale (or risk of autism) when considering only individuals with severe

hypothyroxinemia, because this analysis was not conducted. No increased risk of autism was found for children of mothers positive for TPO Ab.

Table [SEQ Table * ARABIC]. Summary of Key Findings from Román et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Román</Author><Year>2013</Year><RecNum>26</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047642">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Román, G C</author><author>Ghassabian, A</author><author>Bongers-Schokking, J</author><author>Jaddoe, V W V</author><author>Hofman, A </author><author>de Rijke, Y B</author><author>Verhulst, F C</author><author>Tiemeier, H</author></authors></contributors><titles><title>Association of gestational maternal hypothyroxinemia and increased autism risk</title><secondary-title>Annals of Neurology</secondary-title></titles><periodical><full-title>Annals of Neurology</full-title></periodical><pages>733-742</pages><volume>74</volume><number>5</number><section>733</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1002/ana.23976</electronic-resource-num></record></Cite></EndNote>]

Variable	Pervasive Developmental Problems (PDP) β (95% CI), *P*	Social Responsiveness Scale (SRS) β (95% CI), *P*
TSH per SD	0.01 (-0.02, 0.03), 0.68	0.01 (-0.001, 0.01), 0.12
fT4 per SD	-0.03 (-0.06, -0.01), 0.04	-0.002 (-0.01, 0.01), 0.67
Mild hypothyroxinemia	0.09 (-0.02, 0.19), 0.62	0.02 (-0.01, 0.04), 0.33
Only mild hypothyroxinemia	-0.04 (-0.17, 0.004)	-0.02 (-0.06, 0.02), 0.28
Severe hypothyroxinemia	0.23 (0.07, 0.37), 0.04	0.05 (0.01, 0.10), 0.01

Source: Román et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Román</Author><Year>2013</Year><RecNum>26</RecNum><Suffix>`, Table 3</Suffix><DisplayText>(2013, Table 3)</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047642">26</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Román, G C</author><author>Ghassabian, A</author><author>Bongers-Schokking, J</author><author>Jaddoe, V W V</author><author>Hofman, A </author><author>de Rijke, Y B</author><author>Verhulst, F C</author><author>Tiemeier, H</author></authors></contributors><titles><title>Association of gestational maternal hypothyroxinemia and increased autism risk</title><secondary-title>Annals of Neurology</secondary-title></titles><periodical><full-title>Annals of Neurology</full-title></periodical><pages>733-742</pages><volume>74</volume><number>5</number><section>733</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1002/ana.23976</electronic-resource-num></record></Cite></EndNote>].
Notes: Mild hypothyroxinemia (n = 136): 0.03 < TSH < 2.5 mIU/L and fT_4 < 11.82.
Only mild hypothyroxinemia (n = 295): 0.03 < TSH < 2.5 mIU/L and 10.99 < fT_4 < 11.82.
Severe hypothyroxinemia (n = 159): 0.03 < TSH < 2.5 mIU/L and fT_4 < 10.99 pmol/L.
The β's are not interpretable, as the mathematically transformed scores were used in the analysis.

Key finding: Severe maternal hypothyroxinemia at a mean gestational age of 13.4 weeks was significantly associated with an almost four-fold increased risk of being a probable autistic child and a higher score on a scale of autistic symptoms among 6-year-old children.

Other Endpoints

Detailed Summary of Gyllenberg et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA]

Hypothyroxinemia During Gestation and Offspring Schizophrenia in a National Birth Cohort

Gyllenberg et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] examined the relationship between maternal thyroid deficiency during gestation and schizophrenia in offspring with a nested case-control study. Retrospective study data were obtained from the Finnish Prenatal Study of Schizophrenia (FiPS-S), a subset within the Finnish Maternity Cohort (FMC). The FMC contains archived maternal blood samples from most pregnancies in Finland since 1983. Offspring in the cohort with schizophrenia or schizoaffective disorder (both referred to as schizophrenia hereafter) were identified using the Finnish Hospital and Outpatient Discharge Register and were included if they were within the age of risk for schizophrenia. For this study, records were included if the individual was diagnosed at 26 years old or less before December 31, 2009. The national hospital and outpatient information recorded diagnoses for psychiatric hospital admissions and psychiatric outpatient treatment visits and was obtained for FiPS-S participants. Maternal fT4 and TSH were measured via blood samples drawn during the first trimester or early second trimester (2-4 months of pregnancy). TPO Ab was not measured. Blood samples were excluded if they contained HIV, syphilis, or hepatitis.

After cases of schizophrenia were identified, they were matched 1:1 with control subjects. Control subjects were drawn randomly from the FMC if they did not have schizophrenia or other psychotic disorders. Maternal blood serum samples of 1,010 case-control pairs were assessed for fT4, and 948 case-control pairs were assessed for TSH. Maternal thyroid deficiencies measured included hypothyroxinemia (classified as fT4 $\leq 10^{th}$ percentile and TSH outside of the 5^{th}-95^{th} percentile), hypothyroidism, subclinical hypothyroidism, hyperthyroidism, and subclinical hyperthyroidism.

Chi squared, Fisher's exact, and *t*-tests were used to evaluate relationships between covariates, thyroid hormones, and schizophrenia. fT4 levels were log-transformed before being analyzed as continuous variables to correct the skewness of the data. Categorical transformation of continuous variables allowed maternal thyroid disorder data to be interpreted using logistic regression models.

A summary of results from Gyllenberg et al. (2016) regarding the association between maternal hypothyroxinemia and offspring schizophrenia is presented in [REF _Ref512854775 \h]. Maternal hypothyroxinemia was associated with an increased odds of schizophrenia in offspring (OR = 1.75; 95% CI: 1.22-2.50, $p = 0.002$). The proportion of subjects with maternal hypothyroxinemia was 11.8% among schizophrenic subjects compared with 8.6% among control subjects. This association remained significant after adjusting for maternal psychiatric history, province at birth, and maternal smoking status (OR = 1.70; 95% CI: 1.13-2.55; $p = 0.010$).

Defining maternal fT4 as a continuous variable, there was a linear association between log units of maternal fT4 and log odds of schizophrenia in offspring. A conditional logistic regression analysis revealed that the odds of schizophrenia decreased by almost 50% per log unit increase of maternal fT4 (OR = 0.54; 95% CI: 0.31-0.94; $p = 0.028$). This relationship remained significant after adjusting for maternal psychiatric history and province of birth. However, after individually adjusting for

maternal smoking during early gestation and collectively adjusting for maternal psychiatric history, province of birth, and maternal smoking, the association between maternal hypothyroxinemia and offspring schizophrenia was no longer significant. The adjustment for maternal smoking resulted in a greater than 20% change in the odds ratio. According to the authors, "this finding suggests that the relationship between maternal fT4 and schizophrenia is present only when fT4 levels are below a particular threshold" (p. 966, defined in this study as under the 10th percentile of the distribution). The association between log-transformed TSH and schizophrenia was not significant. In analyzing for potential mediators in the association between hypothyroxinemia and schizophrenia, pre-term birth and birthweight both decreased the odds ratios, and the *p*-value was no longer significant.

Table [SEQ Table * ARABIC]. Summary of Results Regarding the Association Between Maternal Hypothyroxinemia and Offspring Schizophrenia

Model	Odds Ratio (95% CI)	*p*-Value
Categorical Hypothyroxinemia[a] During Early Gestation		
Unadjusted	1.75 (1.22-2.50)	0.002
Individually adjusted for maternal psychiatric history	1.92 (1.30-2.83)	0.001
Individually adjusted for province of birth	1.78 (1.23-2.57)	0.002
Individually adjusted for maternal smoking during early gestation[b]	1.62 (1.12-2.37)	0.012
Adjusted for maternal psychiatric history, province of birth, and maternal smoking	1.70 (1.13-2.55)	0.010
Log-Transformed fT4 During Early Gestation		
Unadjusted	0.54 (0.31-0.94)	0.028
Individually adjusted for maternal psychiatric history	0.53 (0.30-0.94)	0.029
Individually adjusted for province of birth	0.57 (0.33-0.999)	0.049
Individually adjusted for maternal smoking during early gestation[b]	0.71 (0.39-1.27)	0.243
Adjusted for maternal psychiatric history, province of birth, and maternal smoking	0.74 (0.40-1.38)	0.342

Source: Gyllenberg et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA].
[a] Defined as fT4 ≤ 14.03 pmol/L (≤10th percentile) and TSH > 0.24-3.38 mIU/L (> 5th-95th percentile).
[b] Based on log-transformed levels of cotinine, a metabolite of nicotine and biomarker of smoking, in maternal sera from FMC.

***Key finding**:* An association between fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range) and odds of schizophrenia diagnosis was found using conditional logistic regression. However, this relationship was attenuated after controlling for smoking. Considering fT4 as a categorical variable demonstrated that hypothyroxinemia during early to mid-gestation was associated with 70% increased odds of schizophrenia diagnosis in offspring of hypothyroxinemic mothers compared to the offspring of non-hypothyroxinemic mothers.

5.3.3 Results of Step 3

[REF _Ref512437248 \h] presents the ROB ratings and tier rank for each study identified. In the overall tier ranking, all studies except for three (Kasatkina et al., 2006; Oken et al., 2003; Pop et al., 1999) were rated as Tier 1, indicating that the majority of identified studies were of high quality. The Oken et al. (2003) and Pop et al. (1999) papers were rated as Tier 2. Both of these studies were rated

as probably high ROB for confounding and for attrition, which was also true for several other studies. The Pop et al. (1999) paper was additionally rated as probably high ROB for exposure assessment because the interassay coefficients of variation for the assay technique were slightly above the EPA's specified maximum of 10%, ranging from 11.1% to 12.2%. Because of this one additional probably high ROB rating, the Pop et al. (1999) paper received a Tier 2 ranking instead of a Tier 1 ranking. Similarly, the Oken et al. (2003) paper was rated as probably high ROB for outcome assessment because, in addition to issues with confounding and attrition, it did not provide evidence of blinding, and thus was ranked as Tier 2. The Kasatkina et al. (2006) paper was the only study rated as Tier 3 (i.e., low quality). This study was rated as definitely high ROB for confounding because it did not adjust for confounders. It was also rated as probably high ROB for three components—attrition, exposure assessment, and outcome assessment—since very few details on methodology were provided in the paper.

In the individual ROB ratings, there were several notable similarities across studies. No studies accounted for all of the primary covariates, and thus none were rated as definitely low ROB for confounding. Similarly, none used the gold standard for fT4 measurement; and the EPA did not assign any definitely low ROB ratings for exposure assessment. The majority of studies were rated as probably high ROB for attrition/exclusion. This is because most studies examined a subset of individuals drawn from a larger cohort, and there were either significant differences in characteristics of respondents and non-respondents or an incomplete non-response analysis. Details on the individual ROB ratings for each study can be found in Appendix E.

Table [SEQ Table * ARABIC]. Risk-of-Bias Ratings and Overall Tier for Each Study

• Tier 1: A study is rated as "definitely low" or "probably low" risk of bias for the majority of questions and is not rated as "definitely high" risk of bias for any question. • Tier 2: Study meets neither criteria for 1st or 3rd tiers. • Tier 3: A study is rated as "definitely high" or "probably high" risk of bias for the majority of questions		ROB Ratings					Did the study provide dose-response information specific to children of hypothyroxinemic pregnant women?	Did the study measure iodine intake in participants?
Ranking	**Study**	Did the study design or analysis account for important confounding and modifying variables?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?		
Tier 1	Endendijk et al. (2017)	-	-	+	+	++	N	N
	Finken et al. (2013)	-	-	+	++	++	N	N
	Ghassabian et al. (2011)	+	-	+	+	++	N	N
	Ghassabian et al. (2014)	+	-	+	-	++	N	N
	Gyllenberg et al. (2016)	+	++	+	++	++	N	N
	Henrichs et al. (2010)	-	-	+	+	+	N	N
	Korevaar et al. (2015)	+	-	+	++	++	N	N
	Modesto et al. (2015)	+	-	+	+	++	N	N
	Moleti et al. (2015)	+	++	+	++	-	N	Y
	Noten et al. (2015)	+	++	+	++	++	N	N
	Oostenbroek et al. (2017)	+	-	+	-	++	N	N
	Pop et al. (2003)	-	++	+	++	++	Y	N
	Roman et al. (2013)	+	-	+	+	++	N	N

• Tier 1: A study is rated as "definitely low" or "probably low" risk of bias for the majority of questions and is not rated as "definitely high" risk of bias for any question. • Tier 2: Study meets neither criteria for 1st or 3rd tiers. • Tier 3: A study is rated as "definitely high" or "probably high" risk of bias for the majority of questions		ROB Ratings					Did the study provide dose-response information specific to children of hypothyroxinemic pregnant women?	Did the study measure iodine intake in participants?
Ranking	**Study**	Did the study design or analysis account for important confounding and modifying variables?	Were outcome data complete without attrition or exclusion from analysis?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?		
Tier 2	Oken et al. (2009)	-	-	+	-	++	N	N
	Pop et al. (1999)	-	-	-	++	++	Y	N
Tier 3	Kasatkina et al. (2006)	--	-	-	-	+	N	N

Key for ROB Ratings:

Definitely Low	Probably Low	Probably High	Definitely High
++	+	-	--

5.3.4 Results of Step 4

After identifying 15 Group 1 studies that are Tier 1 or Tier 2, the EPA evaluated the feasibility of deriving functions for one or more studies to assess the impact that incremental changes in fT4 have on neurodevelopmental outcomes. As explained in the subsequent sections, the studies analyzed were too disparate to conduct a meta-analysis. Ultimately, the EPA focused on five studies, four related to cognition (Pop et al., 1999, 2003, Finken et al., 2013, and Korevaar et al., 2016) and one related to behavior (Endendijk et al., 2017), that could be used to describe how incremental changes in thyroid hormone levels in early pregnancy could result in subsequent changes in neurodevelopment.

Group 1 Studies Not Evaluated Further

Cognition

As described in [REF _Ref491174324 \h], of the 16 Group 1 papers identified, 10 of them evaluate cognition using a variety of tests including various IQ tests, Bayley Scales of Infant Development (mental and psychomotor developmental indices), school performance measures, and other validated tests associated with child cognition (Finken et al., 2013; Ghassabian et al., 2014; Henrichs et al., 2010; Kasatkina et al., 2006; Korevaar et al., 2016; Moleti et al., 2016; Noten et al., 2015; Oken et al., 2009; Pop et al., 1999, 2003). Of these 10 studies, two pairs of studies evaluated the same outcomes with the same test. That is, both Korevaar et al. (2016) and Ghassabian et al. (2014) evaluated child IQ using a non-verbal IQ test (Snijders-Oomen Niet-Verbale Intelligentie Test), and both Pop et al. (1999, 2003) papers used the BSID to conduct their neurodevelopmental assessment. The EPA has determined that dose-response analyses will be performed on Korevaar et al. (2016) and the associated data, and both Pop et al. papers.

The EPA has elected not to conduct dose-response analysis on Ghassabian et al. (2014) because it uses the same dataset used in Korevaar et al. (2016) (i.e., the Generation R Cohort). Korevaar et al. (2016) provide a more comprehensive analysis of the fT4/IQ relationship, and little would be gained by conducting dose-response analysis with the effect estimates presented in the Ghassabian et al. (2014) paper. Further, given that Ghassabian et al. (2014) and Korevaar et al. (2016) are both papers evaluating results from the Generation R cohort, it would be inappropriate to combine their effect estimates given the overlap in the populations evaluated [ADDIN EN.CITE <EndNote><Cite><Author>Dickersin</Author><Year>1992</Year><RecNum>1977</RecNum><DisplayText>(Dickersin & Berlin, 1992)</DisplayText><record><rec-number>1977</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1523366779">1977</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Dickersin, K </author><author>Berlin, JA</author></authors></contributors><titles><title>Meta-analysis: State of the science</title><secondary-title>Epidemiologic Reviews</secondary-title></titles><periodical><full-title>Epidemiologic Reviews</full-title></periodical><pages>154-176</pages><volume>14</volume><dates><year>1992</year></dates><urls></urls></record></Cite></EndNote>].

Moleti et al. (2016) also evaluated fT4's association with IQ but used a different IQ test than Korevaar et al. (2016) did (WISC-IQ vs. Snijders-Oomen Niet-Verbale Intelligentie Test). Moleti et al. (2016) found a consistent positive association between maternal fT4 and VIQ, PIQ, and full-scale IQ in a univariate model though these relationships failed to reach statistical significance (this study had a sample size of less than 60 and is considered a pilot study by the authors). After a critical evaluation of the Moleti et al. (2016) paper, the EPA found it is not possible to conduct dose-response

analysis on this paper because the statistical approach used to estimate the effect estimates in Table 4 of Moleti et al. (2016) is not clear in the paper's methods. Specifically, the authors state "logistic regression models were used to assess the dependence of suboptimal cognitive outcomes (IQ scores < 85, i.e., -1SD) on various explanatory variables and confounders" (Moleti et al., 2016 p. 6). However, the results in Table 4 of Moleti et al. (2016) appear to be an analysis of fT4 and continuous IQ scores, not fT4's effect on suboptimal cognitive outcomes. This is based on the direction of the odds ratios explaining the relationship between both fT4 and urinary iodine with IQ and the conclusion stated by Moleti et al. (2016) that there is a positive association between maternal urinary iodine and full-scale IQ. In addition to the lack of clarity regarding the regression analysis performed in Moleti et al. (2016), there is also a lack of information on any fT4 transformations and functional form. Therefore, the EPA is unable to translate the exp β presented in Table 4 of Moleti et al. (2016) into an effect estimate that can be used to inform the perchlorate MCLG.[19]

It is possible to derive dose-response functions to explain the relationship between maternal fT4 estimates with the CMD at various infant ages based on the data in Kasatkina et al. (2006). However, the EPA has opted to not derive functions from this study because it demonstrated the highest risk of bias of any Group 1 study assessed in the data quality evaluation (Appendix E). There are several reasons for this. First, there was no attempt to evaluate any covariates in the population. It is also unclear how valid and reliable the fT4 measurements were, because no interassay coefficients of variation were reported for the assays used. Similarly, few details were provided on the outcome assessment. The EPA was unable to locate any further information on the methods used to calculate the CMD. Additionally, the results from these analyses are based on fewer than 10 individuals in each age group, and it is unclear if the women represented by the data in the figure were treated with iodine supplementation or not. Lastly, the underlying data for the dose-response function are based on the digitization of figures in the paper, which was done for other analyses. However, the figure's axes were flipped in the original publication, with fT4 as the dependent variable and CMD as the independent variable (i.e., CMD is predicting fT4 instead of fT4 predicting CMD). Given the uncertainties in the analyses, the EPA did not pursue this paper any further.

There are two other papers, Noten et al. (2015) and Oken et al. (2009), that evaluated cognition and were not evaluated for dose-response functions. Noten et al. (2015) evaluated school performance, and Oken et al. (2009) evaluated VRM, PPVT, and WRAVMA. Given that neither of these studies found a significant relationship between maternal thyroid hormone parameters and the cognitive outcomes evaluated in their studies, and that no other study (with which these studies could be combined in a meta-analysis) evaluated the same outcome, it would be difficult to justify using either study to inform an MCLG for perchlorate. Subsequently, neither study was pursued further.

Lastly, analysis was not conducted on Henrichs et al. (2010) given the lack of data needed to conduct the analysis.[20] [REF _Ref491174324 \h] (at the end of Section [REF _Ref517449014 \r \h]) summarizes the EPA's conclusions related to the Group 1 – cognition papers.

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[19] Attempts were made to contact the study authors, and no response was received.

[20] Attempts were made to contact the study authors, and no response was received.

Behavior

In total four papers were located in Group 1 that evaluated maternal fT4 and its relationship with behavioral measures (Endendijk et al., 2017; Ghassabian et al., 2011; Modesto et al., 2015; Oostenbroek et al., 2017). Of these four papers only one was considered for further analysis (Endendijk et al., 2017). Modesto et al. (2015) was not evaluated due to a lack of an association between maternal thyroid hormone levels and ADHD. Given that no other study located evaluated maternal thyroid hormone levels as they relate to ADHD, it would be inappropriate to inform the MCLG based on this singular null finding, and subsequently the EPA did not analyze this paper any further.

Ghassabian et al. (2011) and Endendijk et al. (2017) both used the CBCL to evaluate internalizing and externalizing behaviors. However, the two studies reported their results differently, with Endendijk et al. (2017) noting differences at the subscale level (i.e., anxiety/depression, which are subscales of internalizing behavior) and Ghassabian et al. (2011) evaluating results at the higher level (i.e., internalizing or externalizing). Given the differences in the endpoints evaluated when considering Endendijk et al. (2017) and Ghassabian et al. (2011), it would not be appropriate at this time to combine the effect estimates from these papers to evaluate the relationship between maternal fT4 and child behavioral outcomes. Subsequently, the EPA did not conduct any dose-response modeling based on the Ghassabian et al. (2011) paper.

Oostenbroek et al. (2017) also evaluated maternal thyroid hormones as they relate to behavior using the SDQ. There is potential to derive a dose-response function based on the analysis presented in Oostenbroek et al. (2017). However, the analysis in Oostenbroek et al. (2017) is based on a logistic regression analysis informing an odds ratio. Therefore, to conduct an analysis evaluating how a change in fT4 would impact the change in odds of teacher-reported problem behavior, the baseline odds of teacher-reported problem behavior in the United States are needed [ADDIN EN.CITE <EndNote><Cite><Author>RTI International</Author><Year>2015</Year><RecNum>2024</RecNum><DisplayText>(RTI International, 2015)</DisplayText><record><rec-number>2024</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1533924000">2024</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>RTI International,</author></authors></contributors><titles><title>User's manual - Environmental Benefits Mapping and Analysis Program - Community edition</title></titles><dates><year>2015</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">https://19january2017snapshot.epa.gov/sites/production/files/2015-04/documents/benmap-ce_user_manual_appendices_march_2015.pdf</style></url></related-urls></urls></record></Cite></EndNote>]. The EPA has not identified data on the baseline rate of teacher-reported problem behavior in the United States.[21] Subsequently, the necessary data to derive a

[21] The National Health Interview Survey did include a short version of the SDQ and evaluated outcomes in more than 10,000 U.S. children; however, these are based on parent reports [ADDIN EN.CITE <EndNote><Cite><Author>YouthInMind</Author><Year>2004</Year><RecNum>1978</RecNum><DisplayText>(YouthInMind, 2004)</DisplayText><record><rec-number>1978</rec-number><foreign-

function from Oostenbroek et al. (2017) are not available. A summary of conclusions related to each behavior paper is provided in [REF _Ref512354169 \h].

Autism

Only one Group 1 paper evaluated continuous maternal fT4 as associated with autism (Román et al., 2013). The data needed to inform a dose-response function from this paper (SD) are not available,[22] and subsequently the EPA did not conduct additional modeling based on this paper. The EPA's evaluation of this paper is summarized in [REF _Ref512354178 \h].

Other Endpoints

Gyllenberg et al. (2016) evaluated the relationship between maternal fT4 and schizophrenia. Gyllenberg et al. (2016) found 70% increased odds of schizophrenia diagnosis with maternal hypothyroxinemia. Additionally, they found continuous log maternal fT4 to be associated with schizophrenia (OR = 0.57 (95% CI: 0.33-0.999) when individually adjusted for province of birth and OR = 0.53 (95% CI: 0.30-0.94) when individually adjusted for maternal psychiatric history). However, after adjusting for maternal smoking and psychiatric history, this relationship was attenuated (OR = 0.74 (95% CI = 0.40 -1.38)). Given that no other papers evaluated maternal fT4 and schizophrenia, the EPA has deemed it inappropriate to inform an MCLG based on this study alone given the attenuation of statistical significance with the adjustment for smoking. Therefore, additional analyses were not performed on this paper.

Group 1 Studies Considered for Further Analysis

Five of the 16 Group 1 studies (Pop et al., 1999, 2003; Finken et al., 2013; and Korevaar et al., 2016; Endendijk et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Endendijk</Author><Year>2017</Year><RecNum>1915</RecNum><DisplayText>(2017)</DisplayText><record><rec-number>1915</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503500102">1915</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Endendijk, J.J.</author><author>Wijnen, H.A.</author><author>Pop, V.J.</author><author>van Baar, A.L.</author></authors></contributors><titles><title>Maternal thyroid hormone trajectories during pregnancy and child behavioral problems</title><secondary-title>Hormones and Behavior</secondary-title></titles><periodical><full-title>Hormones and Behavior</full-title></periodical><pages>84-92</pages><volume>94</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>] included data that could be used to quantitatively describe the relationship between thyroid hormone levels in early pregnancy and changes in neurodevelopment. Neurodevelopmental

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keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1523369849">1978</key></foreign-keys><ref-type name="Web Page">12</ref-type><contributors><authors><author>YouthInMind</author></authors></contributors><titles><title>Normative SDQ Data from the USA</title></titles><volume>2018</volume><number>April </number><dates><year>2004</year></dates><urls><related-urls><url><style face="underline" font="default" size="100%">http://www.sdqinfo.org/norms/USNorm.html</style></url></related-urls></urls></record></Cite></EndNote>].

[22] Attempts were made to contact the study authors, and no response was received.

outcomes associated with these studies included assessment of the BSID, a Dutch non-verbal intelligence test (the Snijders-Oomen Niet-Verbale Intelligentie Test), and the standard deviation of reaction time. These studies can be identified in the "EPA Evaluation Column" of [REF _Ref491174324 \h] through [REF _Ref512805292 \h], which states that further analysis was conducted.

Table [SEQ Table * ARABIC]. Summary of Group 1 Study Results Based on Continuous Measure of fT4 – Cognition

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
Intelligence Quotient							
Ghassabian et al. **[ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2014</Year><RecNum>10</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047632">10</key></foreign-keys><ref-**	3,727 Dutch mother-child pairs	No specific data on iodine status provided.	One time during pregnancy (mean: 13.5 GW ± 2 GW, range: 5.7-17.9 GW) (pmol/L)	Nonverbal IQ at 6 years	-0.24 (-0.61, 0.14), fT4 per SD[a]	Maternal hypothyroxinemia during early pregnancy (mean GW = 13.5) was associated with an average reduction of 4.3 points (p = 0.001, 95% CI: -6.68, -1.81) in children's nonverbal IQ at age 6. Continuous measures of maternal thyroid function (TSH, fT4) across the entire range (not the hypothyroxinemic range) and subclinical hypothyroidism were not significantly associated with nonverbal IQ in 6-year-old children.	*Further analysis was not performed* because this study is based on the same dataset as Korevaar et al. (2016), which provided a more comprehensive analysis of the fT4/IQ relationship. Subsequently, efforts to evaluate the fT4/IQ relationship from the Generation R cohort data are based on Korevaar et al. (2016) or the dataset Dr. Korevaar provided to the EPA.

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A</author><author>Marroun, H E</author><author>Peeters, R P</author><author>Jaddoe, V W</author><author>Hofman, A</author><author>Verhulst, F C</author><author>Tiemeier, H</author><author>White, T</author></authors></contributors><titles><title>Dow							

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
nstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2383-2390</pages><volume>99</volume><nu							

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$		Study Summary	EPA Evaluation
mber>7</number><section>2383</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2013-4281</electronic-resource-num></record></Cite></EndNote>] [Tier 1]								
Korevaar et al. **[ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Korevaar</Author><Year>2016</Year><RecNum>313</RecNum><DisplayText>(2016)</DisplayText><record><rec-**	3,839 Dutch mother-child pairs	Yes, urine samples were taken for a random subset of the population (n = 672).	One time in pregnant mother (median: 13.2 GW; range 9-18 GW) (pmol/L)	Child IQ at 6 years[b]	Variable fT4 fT4[2]	β (SE) 33.81 (12.25) -6.235 (2.210)	The authors concluded that both low and high maternal fT4 concentrations during pregnancy were associated with statistically significant lower child IQ and lower gray matter and cortex volume.	*Further analysis was performed* to estimate the incremental impact that doses of perchlorate (using the BBDR model) have on IQ.

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
number>313</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832236">313</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, Tim I. M.</author><author>Muetzel, Ryan</author><author>Me							

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
dici, Marco</author><author>Chaker, Layal</author><author>Jaddoe, Vincent W. V.</author><author>de Rijke, Yolanda B.</author><author>Steegers, Eric A. P.</author><author>Visser, Theo J.</author><author>White, Tonya</author><author>Tiemeier, Henning</author><author>Peeters, Robin P.</author></authors></contributors><titles><title>Association of maternal							

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study</title><secondary-title>The Lancet Diabetes & Endocrinology</secondary-title></titles><periodical><full-title>The Lancet Diabetes & Endocrinology</full-title></periodical><pages>35-43</pages><v							

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
olume>4</volume><number>1</number><dates><year>2016</year></dates><isbn>22138587</isbn><urls></urls><electronic-resource-num>10.1016/s2213-8587(15)00327-7</electronic-resource-num></record></Cite></EndNote>] [Tier 1]							
Moleti et al. **[ADDIN EN.CITE ADDIN EN.CITE.DATA]** [Tier 1]	59 Sicilian mother-child pairs	Yes, urinary iodide excretion measured in random urine samples throughout gestation and from children at time of cognitive evaluation.	Every 6 weeks, from < 12 GW to term (pmol/L)	Child IQ at 6-12 years	fT4 measured ≤ 12 GW[c] 1.192 (0.980, 1.450) [exp β Verbal IQ] 1.053 (0.881, 1.259) [exp β Performance IQ]] 1.103 (0.928, 1.311) [exp β Full-Scale IQ] fT4 measured 13-18 GW 1.217 (1.015 -1.459) [exp β Verbal IQ] 1.010 (0.855 -1.194)	The authors found that maternal iodine status is predictive of neurodevelopmental outcomes in offspring. The relationship between fT4 at various periods of gestation was consistently associated with verbal, performance, and full-scale IQ, but	*Further analysis was not performed* because the description of the statistical methods is not sufficient to allow for the derivation of a dose-response function.[d]

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
					[exp β Performance IQ]] 1.165 (0.980-1.385) [exp β Full-Scale IQ] fT4 measured 19-24 GW 1.234 (0.991-1.537) [exp β Verbal IQ] 1.125 (0.897-1.411) [exp β Performance IQ] 1.155 (0.937-1.425) [exp β Full-Scale IQ] fT4 measured 25-30 GW 1.137 (0.928-1.393) [exp β Verbal IQ] 1.003 (0.810-1.243) [exp β Performance IQ] 1.031 (0.847-1.254) [exp β Full-Scale IQ] fT4 measured GW 31-term 1.191 (0.982-1.445) [exp β Verbal IQ] 1.010 (0.834-1.224) [exp β Performance IQ] 1.070 (0.895-1.280) [exp β Full-Scale IQ]	failed to reach statistical significance.	

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
Bayley Scales (MDI and PDI)							
Pop et al. (1999) [Tier 2]	220 children of Dutch women, 22 of which had fT4 < 10th percentile from iodine-sufficient area	No specific data on iodine status provided.	First and third trimesters of pregnancy (result presented is specific to first trimester (12 GW) of pregnancy) (pmol/L)	Bayley Scales score (PDI) at 10 months Bayley Scales score (MDI) at 10 months	**8.5 (0.01, 17.04)** [e,f] Not reported	Maternal fT4 levels in the lowest 10th percentile in the first trimester among an iodine-sufficient population were significantly associated with reduced psychomotor development in 10-month-old infants.	*Further analysis was performed* to estimate the incremental impact that doses of perchlorate (using the BBDR model) have on PDI. Data were not presented in the paper to allow for analogous analysis of MDI.

Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E	57 children (2 years old) of Dutch women with hypothyroxinemia	No specific data on iodine status provided.	Repeated each trimester of pregnancy (result presented is specific to first trimester (12 GW) of pregnancy) (pmol/L)	Bayley Scales score (PDI) at age 2 years Bayley Scales score (MDI) at age 2 years	**8.4 (4.0, 12.8)**[e] **6.3 (1.9, 10.62)**	Maternal fT4 levels in the lowest 10th percentile in the first trimester were significantly associated with a clinically relevant difference in psychomotor and mental development among 2-year-olds.	*Further analysis was performed* to estimate the incremental impact that doses of perchlorate (using the BBDR model) have on PDI and MDI.

P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><sectio

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
n>282</sectio n><dates><ye ar>2003</year ></dates><urls ></urls></reco rd></Cite></E ndNote>] [Tier 1]							
Other Cognitive Tests							
Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29	1,765 Dutch mother-child pairs	No specific data on iodine status provided.	One time during pregnancy (median: 12.9 GW, interquartile range (IQR): 11.9–14.3) (pmol/L)	Age 5-6 years Baseline Speed Mean reaction time, milliseconds **Reaction time, SD, milliseconds** Pursuit Deviation, millimeters SD of deviation, millimeters Tracking Mean distance, millimeters Accuracy stability, millimeters Movement speed, seconds	 -4.5 (-9.0, 0.1)[g] **-4.9 (-9.5, -0.2)** -0.01 (-0.22, 0.21) 0 (-0.20, 0.21) -0.01 (-0.11, 0.09) 0.04 (-0.06, 0.15) -0.08 (-0.34, 0.18)	Continuous maternal fT4 levels at a median of 12.9 GW were inversely associated with the reaction time variability among 5- to 6-year-old children (an increase in the reaction time SD of 4.9 ms was associated with every 1 pmol/L reduction in maternal fT4). Considering fT4 as a categorical variable demonstrated that there was a 39.5 ms increase in mean reaction time and a 41.2 ms increase in SD of reaction time, when comparing the	*Further analysis was performed* to estimate the incremental impact that doses of perchlorate (using the BBDR model) have on the standard deviation of reaction time.

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced						offspring of hypothyroxinemic to non-hypothyroxinemic mothers.	

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic							

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>] [Tier 1]							
Henrichs et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Henrichs</Author><Year>2010</Year><RecNum>16</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"	2,779 Dutch mother-child pairs	No specific data on iodine status provided.	One time during pregnancy (mean: 13.3 GW ± 1.7 GW) (pmol/L)	Odds of expressive language delay at 18 and 30 months[h] Expressive Language Delay 18 months 30 months 18 and 30 months Nonverbal cognitive delay 30 months	*Odds Ratio*[i] 0.95 (0.83, 1.09), fT4 per SD **0.84 (0.71, 0.99), fT4 per SD** 0.90 (0.80-1.01), fT4 per SD 0.85 (0.72, 1.01), fT4 per SD	Severe maternal hypothyroxinemia was associated with expressive language delay at 18 and 30 months and non-cognitive delay at 30 months. Further, there was an increase in the odds of expressive language delay and non-cognitive delay when comparing the offspring of children exposed to mild versus severe maternal hypothyroxinemia, suggesting a potential dose-response between the severity of hypothyroxinemia and expressive language delay and	*Further analysis was not performed* because the SD needed to translate this result for a regression analysis was not available.

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
timestamp="1432047636">16</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Henrichs, J</author><author>Bongers-Schokking, J J</author><author>Schenk, J J</author><author>Ghassabian, A</author><author>Schmidt, H G</author><author>Visser, T J</author><author>Hooijkaas, H</author><author>de Muinck Keizer-Schrama, S M						non-cognitive delay. Additionally, maternal fT4 levels per SD were associated with a reduction in odds of expressive language delay at 30 months (OR = 0.84 per SD of fT4).	

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
P F</author><author>Hofman, A</author><author>Jaddo, V V W</author><author>Visser, W</author><author>Steegers, E A P</author><author>Verhulst, F C</author><author>de Rijke, Y B</author><author>Tiemeier, H</author></authors></contributors><titles><title>Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study</title><s							

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
econdary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>4227-4234</pages><volume>95</volume><number>9</number><section>4227</section><dates><year>2010</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2010-0415</electronic-resource-							

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
num></record></Cite></EndNote>] [Tier 1]							
Kasatkina et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Kasatkina</Author><Year>2006</Year><RecNum>1976</RecNum><DisplayText>(2006)</DisplayText><record><rec-number>1976</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1522434753">1976</key></foreign-keys><ref-type	24 Russian mothers (13 hypothyroxinemic)	No, however authors note the study population is in an iodine-deficient region.	5 - 9 GW fT4 < 10th percentile	CMD reduction in offspring of hypothyroxinemic mothers	6 months[i] **$r = 0.684$, $p = 0.020$** 9 months **$r = 0.629$, $p = 0.038$** 12 months **$r = 0.708$, $p = 0.014$**	The authors found maternal fT4 levels in early pregnancy correlated significantly with CMD in children at ages 6, 9, and 12 months.	*Further analysis was not performed* on fT4's impact on CMD scores. Although the derivation of a function is possible based on the data presented in the paper, there is a very high risk of bias associated with this paper along with major uncertainties that limit its usefulness.

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
name="Journal Article">17</ref-type><contributors><authors><author>Kasatkina, E.P.</author><author>Samsonova, L.N.</author><author>Ivakhnenko, V.N.</author><author>Ibragimova, G.V.</author><author>Ryabykh, A.V.</author><author>Naumenko, L.L.</author><author>Evdokimova, Y.A.</author></authors></contributors><titles><title>Gestational hypothyroxinemia and cognitive							

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
function in offspring</title><secondary-title>Neuroscience and Behavioral Physiologogy</secondary-title></titles><periodical><full-title>Neuroscience and Behavioral Physiologogy</full-title></periodical><pages>619-624</pages><volume>36</volume><number>6</number><dates><year>2006</year></dates><urls></urls></record></Cite></EndNote>] [Tier 3]							
Noten et al. [**ADDIN EN.CITE**	1,196 Dutch mother-child pairs	No specific data on	One time in pregnant mother,	Odds of poor school performance at 5 years	Odds Ratio	Maternal hypothyroxinemia at the end of the first	*Further analysis was not performed.* While the

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
ADDIN EN.CITE.DATA] [Tier 1]		iodine status provided.	(mean: 12.9 GW; range 11.9-14.3) (pmol/L)	Arithmetic Test Poor school performance fT4, continuous -Unadjusted -Adjusted[k] Arithmetic Test Subnormal school performance fT4, continuous -Unadjusted -Adjusted[k] Language Test Poor school performance fT4, continuous -Unadjusted -Adjusted[k] Language Test Subnormal school performance fT4, continuous -Unadjusted -Adjusted[k]	 0.88 (0.77, 1.02) 0.92 (0.80, 1.07) **0.89 (0.81, 0.98)** 0.92 (0.83, 1.02) 0.95 (0.84, 1.08) 1.02 (0.90, 1.16) 0.98 (0.90, 1.08) 1.02 (0.93, 1.13)	trimester was associated with reduced arithmetic test performance in 5-year-old offspring. Inverse probability weighting demonstrates that non-response bias may be present in this study, and thus the authors caution that the results should be interpreted with caution.	relationship between maternal fT4 as a continuous variable and odds of subnormal arithmetic performance was observed, this relationship diminished with the adjustment of confounders and with inverse probability weighting. No other studies related maternal fT4 as a continuous variable to subpar school performance, thus, it would not be feasible to conduct a meta-analysis on this outcome to inform an MCLG for perchlorate.

Oken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Year>2009</Year><RecNum>22</RecNum><DisplayText>(2009)</DisplayText><record><rec-number>22</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047640">22</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oken, E</author><author>Braverman, L</author><author>Platek,	500 mother-child pairs in Massachu-setts	No specific data on iodine status provided.	One time in pregnant mother (mean: 10.2 GW) (Total T4: µg/dL)	Age 6 months Visual Recognition Memory Peabody Picture Vocabulary Test Wide Range Assessment of Visual Motor Ability	-0.04 (-0.8, 0.7) [T4][l] -0.1 (-0.7, 0.5) [T4][l] 0.004 (-0.6, 0.6) [T4][l]	Neonatal total T4 levels within the euthyroid range were not predictive of cognitive outcome, nor were they associated with maternal T4 levels. Maternal thyroid function (T4, TSH, TPO Ab measured at approximately 10 GW) was not associated with any of the neurodevelopmental outcomes assessed. This study did not make an attempt to separately analyze hypothyroxinemic maternal-child pairs.	*Further analysis was not performed* because the study did not find an association between maternal thyroid hormone levels and VRM, visual motor ability, or fine motor skills. No other studies related maternal thyroid hormones as a continuous variable with VRM, PPVT or WRAVMA; thus, it would not be feasible to conduct a meta-analysis on these outcomes to inform an MCLG for perchlorate.

D</author><author>Mitchell, M L</author><author>Lee, S L</author><author>Pearce, E N</author></authors></contributors><titles><title>Neonatal thyroxine, maternal thyroid function, and child cognition</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>497-503</pages><volume>94</volume><number>2</number

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
><section>497</section><dates><year>2009</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2008-0936</electronic-resource-num></record></Cite></EndNote>] [Tier 2]							

[a] Model adjusted for ethnicity, birth order, maternal age, BMI, marital status, maternal history of smoking, educational levels, maternal psychopathology during pregnancy, household income, and gestational age at time of thyroid sampling.

[b] Model adjusted for gestational age, maternal age, smoking, BMI, parity, education level, ethnic origin, fetal sex, and birthweight.

[c] Model adjusted for maternal age; gestational age at birth; birthweight; child age at time of IQ test; maternal fT4, fT4, and TSH various times during gestation; maternal urinary iodide excretion; family socioeconomic status; maternal parity; sex of child; breastfeeding; major maternal stressful life events; and maternal/parental education.

[d] Attempts have been made to contact study authors with no success.

[e] Based on digitization of figures representing correlation analysis presented in the paper.

[f] Model adjusted for maternal depression, psychosocial factors, tobacco and alcohol use during pregnancy, and demographic variables.

[g] Model adjusted for age, gender, demographic characteristics (e.g., birth order, ethnicity) and pregnancy characteristic (e.g., BMI and diabetes).

[h] Expressive language delay at 30 months was defined as an expressive vocabulary score below the 15th age- and gender-specific percentile or no word combinations

[i] Model adjusted for maternal age, education, pre-natal distress, pre-natal smoking, birthweight, gestational age at blood sampling, and child ethnicity.

[j] Covariates, confounders, and any model adjustments were not displayed in the study.

[k] Model adjusted for maternal education, ethnicity, BMI, and depressive symptomatology.

[l] Model adjusted for gestation length, age at testing, sex, maternal education, and ethnicity.

Table [SEQ Table * ARABIC]. Summary of Group 1 Study Results Based on Continuous Measure of fT4 – Behavior (including attention-related and problem behavior)

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation

Endendijk et al. **[ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Endendijk</Author><Year>2017</Year><RecNum>1915</RecNum><DisplayText>(2017)</DisplayText><record><rec-number>1915</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503500102">1915</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>E**	442 Dutch pregnant mother-child pairs	No specific data on iodine status provided.	12, 24, 36 GW (pmol/L)	Child behavior problems as measured by internalizing scores *(anxiety/depression)* from the CBCL assessment (fT4 measured at 12GW)	**-0.12** [a,b]	The authors reported a significant effect of first-trimester fT4 on anxiety/depression or internalizing behaviors. The authors also evaluated the trajectory of thyroid hormone levels as they related to the prediction of anxiety/depression and determined that including the trajectory of fT4 in the first-trimester model improved the prediction of child anxiety/depression scores.	*Further analysis was performed* to evaluate first-trimester fT4 concentration and incremental changes in anxiety/depression as measured by the CBCL

ndendijk, J.J.</author> <author>Wijn en, H.A.</author> <author>Pop, V.J.</author> <author>van Baar, A.L.</author> </authors></c ontributors>< titles><title>M aternal thyroid hormone trajectories during pregnancy and child behavioral problems</titl e><secondar y- title>Hormon es and Behavior</se condary- title></titles> <periodical>< full- title>Hormon es and Behavior</full - title></periodi cal><pages>8 4- 92</pages><v

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
olume>94</volume><dates><year>2017</year></dates><urls></urls></record></Cite></EndNote>] [Tier 1]							

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
Ghassabian et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] [Tier 1]	3,736 Dutch mother-child pairs	No specific data on iodine status provided.	Mean 13.3 GW	Child behavior problems as measured by the CBCL assessment	Effect estimates are beta per SD[c]	Neither maternal fT4 nor maternal hypothyroxinemia was associated with higher child internalizing and externalizing scores at 1.5 and 3 years of age.	*Further analysis was not performed* because no relationship was found between maternal fT4 and internalizing and externalizing behaviors. Although Endendijk et al. (2017) also utilized the CBCL, the effect estimates reported in the paper varied from those reported in Ghassabian et al. (2011), and therefore the estimates could not be combined.
				Internalizing Scores			
				fT4 (mother report; 1.5 and 3 years)	0.03 (-0.11, 0.7)		
				fT4 (father report; 3 years)	-0.07 (-0.025, 12)		
				fT4 (both parents report; 1.5 and 3 years)	0.01 (-0.13, 0.15)		
				Hypothyroxinemia	-0.19 (-0.75, 0.37)		
				Externalizing Scores			
				fT4 (mother report; 1.5 and 3 years)	0.02 (-0.16, 0.20)		
				fT4 (father report; 3 years)	-0.14 (-0.39, 0.11)		
				fT4 (both parents report; 1.5 and 3 years)	-0.02 (-0.16, 0.20)		
				Hypothyroxinemia	0.17 (-0.53, 0.87)		

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
Modesto et al. **[ADDIN EN.CITE ADDIN EN.CITE.DATA]** [Tier 1]	127 Dutch mother-child pairs	No specific data on iodine status provided.	One time in pregnant mother (mean: 13.6 GW; range 6.6-17.9) (result presented is specific to mothers with TH measured < 13 GW) (ng/dL)	Parent-reported ADHD index scores of offspring at 8 years old *Parent Reported ADHDi Score* fT4 Level per SD -Unadjusted -Adjusted for age and sex -Fully adjusted model[d] fT4 per SD (gestational age < 13 weeks -Unadjusted -Adjusted for age and sex -Fully adjusted model[d]	 -0.01 (-0.02, 0.01) -0.004 (-0.02, 0.01) -0.01 (-0.02, 0.01) -0.02 (-0.04, -0.004) -0.02 (-0.04, -0.001) -0.02 (-0.03, 0.003)	Maternal hypothyroxinemia in early pregnancy was associated with higher ADHDi scores in 8-year-old children compared with non-exposed children, after adjusting for confounders (7% increase in ADHDi scores (95% CI: 3%-15%)). When considering fT4 as a continuous variable, the association between maternal fT4 and offspring ADHDi scores was attenuated with the adjustment of confounders.	*Further analysis was not performed* because no relationship was found between a continuous measure of maternal fT4 and neurodevelopment. No other studies related maternal fT4 as a continuous variable to ADHD or parent-reported oppositional scale; thus, it would not be feasible to conduct a meta-analysis on this outcome to inform an MCLG for perchlorate.

Oostenbroek et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Oostenbroek</Author><Year>2017</Year><RecNum>1914</RecNum><DisplayText>(2017)</DisplayText><record><rec-number>1914</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503499994">1914</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Oostenbroek, M.H.W.</author><author>Ker	200 Dutch hypothyroxinemic mother-child pairs	No specific data on iodine status provided.	Median 12.9 GW (IQR: 11.9-14.1 GW) fT4<5th percentile (<7.75 pmol/L) and fT4<10th percentile (<8.15 pmol/L)	*Total problems* Parent reported - Unadjusted OR - Fully adjusted OR[e] Teacher reported - Unadjusted OR - Fully adjusted OR[e] *Hyperactivity/inattention* Parent reported - Unadjusted OR - Fully adjusted OR[e] Teacher reported - Unadjusted OR - Fully adjusted OR[e] *Emotional problems* Parent reported - Unadjusted OR - Fully adjusted OR[e] Teacher reported - Unadjusted OR - Fully adjusted OR[e] *Conduct problems* Parent reported - Unadjusted OR - Fully adjusted OR[e] Teacher reported - Unadjusted OR - Fully adjusted OR[e] *Peer relationship problems* Parent reported	 1.05 (0.91, 1.22) 1.10 (0.96, 1.27) 0.85 (0.76, 0.96) 0.89 (0.79, 1.00) 0.97 (0.86, 1.09) 1.01 (0.90, 1.13) 0.91 (0.82, 1.01) 0.95 (0.85, 1.05) 1.03 (0.90, 1.18) 1.07 (0.93, 1.22) 1.03 (0.90, 1.18) 1.07 (0.93, 1.22) 0.92 (0.82, 1.03) 0.94 (0.84, 1.05) 1.2[p] (0.92, 1.13) 1.04 (0.94, 1.15)	Maternal hypothyroxinemia <5th percentile was associated with a 1.70 (95% CI: 1.01–2.86) increased odds of teacher-reported hyperactivity/ inattention after adjustment for confounders. By increasing the cut-off level to<10th percentile, the odds ratio became 1.47 (95% CI: 0.99–2.20). There were no associations between maternal thyroid function parameters as continuous variables and hyperactivity/ inattention as reported by parents, nor with teacher or parent reports of other types of problem behavior.	*Further analysis was not performed.* Although a borderline statistically significant association was found between teacher-reported problem behavior and maternal fT4 additional data needs, the baseline rate of teacher-reported problem behavior in the United States is needed.

sten, R.H.J.</author><author>Tros, B.</author><author>Kunst, A.E.</author><author>Vrijkotte, T.G.M.</author><author>Finken, M.J.J.</author></authors></contributors><titles><title>Maternal hypothyroxinaemia in early pregnancy and problem behavior in 5-year-old offspring</title><secondary-title>Psychoneuroendocrinology</secondary-title></titles><periodical><full-title>Psychoneuroendocrinology</full-title></periodical><pages>29-35</pages><volume>81</vol	- Unadjusted OR - Fully adjusted OR[e] Teacher reported - Unadjusted OR - Fully adjusted OR[e] *Prosocial problem behavior* Parent reported - Unadjusted OR - Fully adjusted OR[e] Teacher reported - Unadjusted OR - Fully adjusted OR[e]	0.99 (0.89, 1.10) 1.02 (0.92, 1.14) 1.04 (0.93, 1.18) 1.07 (0.95, 1.20) 1.02 (0.93, 1.13) 1.03 (0.93, 1.14) 1.02 (0.94, 1.11) 1.03 (0.95, 1.12)

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
ume><dates> <year>2017</year></dates> urls></urls></record></Cite> </EndNote>] [Tier 1]							

[a] The study authors were contacted about the sign on this beta because they state that lower fT4 is associated with more anxiety/depression, but the beta in the paper is positive (higher fT4 is related to higher CBCL scores). The opposite is expected, as indicated here.

[b] Model adjusted for gestational age and weight at birth, child age at time of CBCL assessment, parity, breastfeeding, mother's age, maternal psychopathology symptoms (pre-natal and at time of CBCL assessment), smoking and alcohol use during pregnancy, educational level, and TPO Ab positivity.

[c] Model adjusted for maternal age, educational level and psychopathology, child's gender and ethnicity, mode of delivery and gestational age at the time of thyroid sampling.

[d] Model adjusted for child age, sex, ethnic background, and parity, and maternal education level, smoking history, psychopathologic symptoms in pregnancy, age, marital status, household income, BMI, and gestational age at the time of blood sampling for maternal thyroid function data.

[e] Model adjusted for ethnicity, years of education, pre-pregnancy BMI, hypertension, smoking during pregnancy of at least one cigarette per day, and anxiety level.

Table [SEQ Table * ARABIC]. Summary of Group 1 Study Results Based on Continuous Measure of fT4 – Autism

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
Román et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Román</Author><Year>2013</Year><RecNum>26</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>26</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047642">26</key></foreign-keys><ref-type name="Journal Article">17</re	4,039 children of mothers in the Netherlands	No specific data on iodine status provided.	One time during pregnancy (mean: 13.4 weeks) (pmol/L)	Age 6 years *Pervasive Developmental Problems* Borderline fT4 per SD Clinical fT4 per SD	 0.93 (0.80, 1.09)[a] 0.95 (0.77, 1.17)[a]	Severe maternal hypothyroxinemia at a mean gestational age of 13.4 weeks was significantly associated with an almost four-fold increased risk of being a probable autistic child and a higher score on a scale of autistic symptoms among 6-year-old children.	*Further analysis was not performed* because the authors cautioned that the betas relating the continuous measure of maternal fT4 and PDP or SRS scale scores were not interpretable because mathematically transformed scores were used in the analyses and the SD needed for analysis was not provided.

f-type><contributors><authors><author>Román, G C</author><author>Ghassabian, A</author><author>Bongers-Schokking, J</author><author>Jaddoe, V W V</author><author>Hofman, A</author><author>de Rijke, Y B</author><author>Verhulst, F C</author><author>Tiemeier, H</author></authors></contributors><titles><title>Association of gestational maternal hypothyroxinemia and increased autism risk</title><secondary-title>Annals of

Neurology</secondary-title></titles><periodical><full-title>Annals of Neurology</full-title></periodical><pages>733-742</pages><volume>74</volume><number>5</number><section>733</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1002/ana.23976</electronic-resource-num></record></Cite></EndNote>]
[Tier 1]

[a] Model was adjusted for child's sex, ethnicity, gestational age at birth, and birthweight, maternal age, educational level, smoking history, pre-natal psychopathology, thyroid medication during pregnancy, parity, marital status, folate and C-reactive levels in early pregnancy, time of thyroid sampling, and paternal age. According to the study authors "the betas are not interpretable, as mathematically transformed scores were used in the analyses" (p.6).

Table [SEQ Table * ARABIC]. Summary of Group 1 Study Results Based on Continuous Measure of fT4 – Other Outcomes

Study [ROB Tier]	Study Population	Iodine Status Assessed	Timing of Maternal Thyroid Hormone Sampling (Units)	Endpoints	Effect Estimates [β based on untransformed fT4, unless otherwise noted] (95 % CI) Underlined & Bold indicate statistically significant at $p < 0.05$	Study Summary	EPA Evaluation
Gyllenberg et al. **[ADDIN EN.CITE ADDIN EN.CITE.DATA]** [Tier 1]	1,010 Finnish mother-child pairs	No specific data on iodine status provided.	One time during pregnancy (2-4 months pregnancy) (pmol/L)	Odds of diagnosis of schizophrenia/ schizoaffective disorder *Log-Transformed fT4 During Early Gestation* Unadjusted Individually adjusted for maternal psychiatric history Individually adjusted for province of birth Individually adjusted for maternal smoking during early gestation Adjusted for maternal psychiatric history, province of birth, and maternal smoking	Various Ages[a] **0.54 (0.31, 0.94)** **0.53 (0.30, 0.94)** **0.57 (0.33, 0.999)** 0.71 (0.39, 1.27) 0.74 (0.40, 1.38)	An association between fT4 as a continuous variable across the entire fT4 range (i.e., not just the hypothyroxinemic range) and odds of schizophrenia diagnosis was found using conditional logistic regression. However, this relationship was attenuated after controlling for smoking. Considering fT4 as a categorical variable demonstrated that hypothyroxinemia during early to mid-gestation was associated with 70% increased odds of schizophrenia diagnosis in offspring of hypothyroxinemic mothers compared to the offspring of non-hypothyroxinemic mothers.	*Further analysis was not performed.* While the relationship between maternal fT4 as a continuous variable and odds of offspring schizophrenia diagnosis was observed, statistical significance was lost after adjustment for confounders. No other studies related maternal fT4 as a continuous variable to risk of schizophrenia, thus, it would not be feasible to conduct a meta-analysis on this outcome to inform an MCLG for perchlorate.

[a] Fully adjusted model adjusted for maternal psychiatric history, province of birth, and maternal smoking.

5.4 Findings Related to Categorical Analyses Supporting MCLG Development Based on Avoiding Hypothyroxinemia

Given the SAB's recommendation to concentrate on sensitive populations, one of which is the fetuses of hypothyroxinemic mothers, it is also useful to evaluate the impact of maternal hypothyroxinemia as evaluated by the studies identified in both Group 1 and Group 2 (keeping in mind that some Group 1 studies included analysis on both continuous and categorical measures of fT4). That is, in Section [REF _Ref482192446 \n \h], the evaluation of the papers was specific to the concentration-response functions present in the analyses based on a continuous measure of thyroid hormone levels. However, of specific interest may be how neurodevelopmental outcomes vary when comparing offspring of hypothyroxinemic mothers to those of non-hypothyroxinemic mothers. [REF _Ref482284683 \h] presents a summary of the findings of studies that evaluate the impact of maternal hypothyroxinemia, as a categorical variable, on adverse neurodevelopmental outcomes in offspring, including IQ score and performance on the BSID.

Evaluating these results as a whole demonstrates that in different populations, at different ages for neurodevelopmental assessment, and at various cut points for fT4, there is a significant difference in performance on global cognitive tests when comparing the offspring of hypothyroxinemic women to those of non-hypothyroxinemic women (Costeira et al., 2011; Ghassabian et al., 2014; Júlvez et al., 2013; Korevaar et al., 2016; Li et al., 2010; Pop et al., 1999, 2003). These findings are supported by several systematic reviews and meta-analyses including Fan and Wu [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Fan</Author><Year>2016</Year><RecNum>307</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>307</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832068">307</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Fan, X.</author><author>Wu, L.</author></authors></contributors><auth-address>a General Surgery Department and.
b Department of Obstetrics and Gynecology , Central People's Hospital of Siping , Siping , China.</auth-address><titles><title>The impact of thyroid abnormalities during pregnancy on subsequent neuropsychological development of the offspring: a meta-analysis</title><secondary-title>Journal of Maternal-Fetal & Neonatal Medicine</secondary-title></titles><periodical><full-title>Journal of Maternal-Fetal & Neonatal Medicine</full-title></periodical><pages>3971-6</pages><volume>29</volume><number>24</number><keywords><keyword>Hypothyroxinaemia</keyword><keyword>meta-analysis</keyword><keyword>neuropsychological development</keyword><keyword>pregnancy</keyword><keyword>subclinical hypothyroidism</keyword><keyword>thyroid peroxidase antibodies</keyword></keywords><dates><year>2016</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>1476-4954 (Electronic)
1476-4954 (Linking)</isbn><accession-num>26988121</accession-num><urls><related-urls><url><style face="underline" font="default" size="100%">http://www.ncbi.nlm.nih.gov/pubmed/26988121</style></url></related-urls></urls><electronic-resource-num>10.3109/14767058.2016.1152248</electronic-resource-num></record></Cite></EndNote>], Wang et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA], and Thompson et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Thompson</Author><Year>2018</Year><RecNum>1956</RecNum><DisplayText>(2018)</DisplayText><record><rec-number>1956</rec-number><foreign-keys><key

app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1516819485">1956</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Thompson, William</author><author>Russell, Ginny</author><author>Baragwanath, Genevieve</author><author>Matthews, Justin</author><author>Vaidya, Bijay</author><author>Thompson-Coon, Jo</author></authors></contributors><titles><title>Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis</title><secondary-title>Clinical endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><dates><year>2018</year></dates><isbn>1365-2265</isbn><urls></urls></record></Cite></EndNote>]. Fan and Wu (2016) and Wang et al. (2016) found that hypothyroxinemia was associated with a 5.7-point lower score on intelligence tests and a three-fold increased risk of delayed cognitive development in children, respectively. Thompson et al. (2018) found that maternal hypothyroxinemia is associated with increased risk of cognitive delay, intellectual impairment, or lower scores on performance tests, but they did not find this association with ADHD or autism.

The only studies that did not find a statistically significant effect on any of the evaluated endpoints in [REF _Ref482284683 \h] are Grau et al. (2015) and Hales et al. (2018). As previously discussed Grau et al. (2015) has a high hypothyroxinemic cut point (13.7 pmol/L), and individuals are not iodine deficient. Hales et al. (2018) hypothesizes that the lack of congruence in their findings may be related to varying definitions of suboptimal thyroid function, lack of universal pregnancy-specific reference ranges for thyroid function tests, and the application of various tools to measure cognition in children across the age spectrum.

Additionally, studies identified in the literature review that are not summarized in [REF _Ref482284683 \h] also associated maternal hypothyroxinemia with an offspring's increased risk of schizophrenia (Gyllenberg et al., 2016), ADHD (Modesto et al., 2015), expressive language delay (Henrichs et al., 2010), and other outcomes (Finken et al., 2013; Kooistra et al., 2006; Noten et al., 2015; Päkkilä et al., 2015; Román et al., 2013; van Mil et al., 2012; Oostenbroek et al., 2017). These studies demonstrate the sensitivity of the offspring of hypothyroxinemic mothers to adverse neurodevelopmental effects. An approach to inform the derivation of an MCLG based on avoiding hypothyroxinemia is presented in Section [REF _Ref517616944 \r \h].

Table [SEQ Table * ARABIC]. Summary of Studies That Compared Neurodevelopment Outcomes (BSID or IQ) in the Offspring of Hypothyroxinemic (hX) and Non-Hypothyroxinemic Mothers

Study	Population	Definition of hX for result (pmol/L unless otherwise noted)	Definition of Reference Group	Statistical method	Age of Neurodevelopmental Assessment	Difference in Score When Comparing hX Population to Reference (95% CI)	*p*-value	Gestational Week of Thyroid Hormone Measurement
MDI Score Using BSID								
Costeira et al. 2011	Portuguese mother-child pairs from iodine-deficient region	fT4 < 10th percentile (< 11.6) (n = 8)	tT4, fT4, tT3, and fT3 between 50th to 90th percentile (n = 36)	t-test on difference between mean scores[a]	24 months	-10.8 (CI: NR) points lower MDI in hX group	> 0.05	< 15
Júlvez et al. 2013	Spanish mother-child pairs	fT4 < 10th percentile (< 8.89) (n = 164)[b]	fT4 > 10th percentile (n = 1,643)	multivariate linear regression[c]	14 months	-2.2 (-4.47, -0.01) points lower MDI in hX group	NR	Median 13, range 8-20
Li et al. 2010	Chinese mother-child pairs	tT4 < 101.79 nmol/L (n = 19)	matched controls with tT4 > 101.79 nmol/L (n = 38)	t-test on difference between mean scores	25-30 months	-9.3 points lower MDI in hX group	0.004	16-20
Pop et al. 1999	Dutch mother-child pairs	fT4 < 10th percentile (10.4) (n = 22) at 12 GW	fT4 >10th percentile (10.4 pmol/L) (n = 198)	t-test on difference between mean scores[d]	10 months	NR because did not find a statistically significant difference	NR	12
Pop et al. 2003	Dutch mother-child pairs	fT4 < 10th percentile (12.4 pmol/L) (n = 57)	fT4 > 10th percentile (12.4 pmol/L) (n = 58)	t-test on difference between mean scores	12 months	-10 (-4, -16) points lower MDI in hX group	0.004	12

Study	Population	Definition of hX for result (pmol/L unless otherwise noted)	Definition of Reference Group	Statistical method	Age of Neurodevelopmental Assessment	Difference in Score When Comparing hX Population to Reference (95% CI)	*p*-value	Gestational Week of Thyroid Hormone Measurement
PDI Using BSID								
Costeira et al. 2011	Portuguese mother-child pairs from iodine-deficient region	fT4 < 10th percentile (< 11.6) (n = 8)	tT4, fT4, tT3, and fT3 between 50th to 90th percentile (n = 36)	t-test on difference between mean scores[a]	24 months	-13.6 (CI: NR) points lower PDI score in hX group	< 0.05	< 15
Júlvez et al. 2013	Spanish mother-child pairs	fT4 < 10th percentile (< 8.89) (n = 164)[b]	fT4 > 10th percentile (n = 1,643)	multivariate linear regression[c]	14 months	0.28 (-1.94 to 2.51) points higher in PDI score in hX group	NR	Median 13, range 8-20
Li et al. 2010	Chinese mother-child pairs	tT4 < 101.79 nmol/L (n = 19)	matched controls with tT4 > 101.79 nmol/L (n = 38)	t-test	25-30 months	-7.6 (CI: NR) points lower PDI score in hX group	0.007	16-20
Pop et al. 1999	Dutch mother-child pairs	fT4 < 10th percentile (10.4) (n = 22) at 12 GW	fT4 >10th percentile (10.4 pmol/L) (n = 198)	t-test on difference between mean scores[d]	10 months	-7.4 (-1.1, -13.9) points lower PDI score in hX group	NR	12
Pop et al. 2003	Dutch mother-child pairs	fT4 < 10th percentile (12.4 pmol/L) (n = 57)	fT4 > 10th percentile (12.4 pmol/L) (n = 58)	t-test on difference between mean scores	24 months	-10 (-6, -16) points lower PDI score in hX group	0.005	12
Intelligence Quotient								
Ghassabian et al. 2014	3,727 Dutch mother-child pairs	fT4 < 5th percentile (< 10.99)	fT4 > 5th percentile (> 10.99 pmol/L) (n = 3,598)	multivariate linear regression	6 years	-4.32 (-6.68, -1.81) IQ points lower in hX group[e]	0.001	mean 13.5, range 5.1–17.9

Study	Population	Definition of hX for result (pmol/L unless otherwise noted)	Definition of Reference Group	Statistical method	Age of Neurodevelopmental Assessment	Difference in Score When Comparing hX Population to Reference (95% CI)	*p*-value	Gestational Week of Thyroid Hormone Measurement
		(n = 129)						
Grau et al. 2015	289 Spanish mother-child pairs	fT4 < 10th percentile (< 13.7) (first trimester) (n = 42)	Urinary iodide concentration >150 g/L, fT4 > 10th percentile and TPO Ab negative (n = 39)	Multivariate ANOVA	1 year	2.7 (CI: NR) IQ points higher in the hX mothers[f]	0.419	end of the 1st trimester
Hales et al. 2018	331 UK mother-child pairs	fT4 < 2.5th percentile[g] (n = 81)	fT4 > 2.5th percentile (n = 232)	Univariate and multivariate logistic regression	7.00–10.92 years	No difference between mean IQ scores of hX children, and those born to mothers with normal thyroid hormone function[h]	0.875	< 16 weeks
Korevaar et al. 2016[i]	3,839 Dutch mother-child pairs	≤ 10th percentile (n = 386)	fT4 between 10th and 90th percentile (n = 3,288)[j]	Multivariate ANOVA	Median 6 years (range 5.6-7.9 years)	-1.8 (0, -3.2) point loss in low fT4 group compared to control group[k]	0.05	9-18

NR = not reported; hX = hypothyroxinemia; GW = gestational weeks.

[a] Model adjusted for maternal age, parity, socioeconomic-cultural status, length of breastfeeding, use of alcohol and tobacco during pregnancy, children's sex, gestational age, type of delivery, Apgar score, birthweight, body length, and head circumference.

[b] n for each group is estimated based on the knowledge that analysis is for individuals with fT4 less than 10th percentile and there are 1,642 people in the regression analysis.

[c] Results adjusted for region, sex, psychologist administering IQ test, gestational age and weight at birth, circulating vitamin D during pregnancy and year –season of sampling, urine cotinine levels during pregnancy, TSH, maternal education, parental social class, quality of the test, and child neurologic pathology.

[d] Model adjusted for maternal depression, psychosocial factors, tobacco and alcohol use during pregnancy, and demographic variables.

[e] Model adjusted for ethnicity, birth order, maternal age, BMI, marital status, maternal history of smoking, educational levels, maternal psychopathology during pregnancy, household income, and gestational age at time of thyroid sampling.

[f] Results from first trimester, total mean WISC, Table 4 of Grau et al. (2015).

[g] The value of the hypothyroxinemic cut point was not identified in the paper.

Study	Population	Definition of hX for result (pmol/L unless otherwise noted)	Definition of Reference Group	Statistical method	Age of Neurodevelopmental Assessment	Difference in Score When Comparing hX Population to Reference (95% CI)	*p*-value	Gestational Week of Thyroid Hormone Measurement

[h] Model adjusted for child sex, age of mothers at birth of offspring, child breastfeeding, schooling (Welsh- or English-medium school attended), place of assessment (home or research center), and socioeconomic status. The overall difference between groups is not reported in Supplementary Table 2 of Hales et al. (2018).

[i] Data are taken from Supplemental Figure 2 of Korevaar et al. (2016).

[j] Reference group is calculated as the total population without the mothers less than or equal to the 10th percentile, and after exclusion of women with *in vitro* fertilization treatment (N = 76) or women with known thyroid disorders or thyroid-interfering medication usage (N = 89). Data are taken from Supplemental Figure 2.

[k] Model adjusted for gestational age, maternal age, smoking, BMI, parity, education level, ethnic origin, fetal sex, and birthweight.

5.5 Summary of Literature Review Findings to Connect Alterations in Thyroid Hormone Levels to Alternations in Neurodevelopment

In this literature review, 16 papers were identified as potentially having data or presenting analysis that may inform the quantitative understanding of the incremental changes in thyroid hormone levels and subsequent adverse neurodevelopmental outcomes. Of these 16 papers, 5 were deemed useful for further quantitative analysis (see [REF _Ref491174324 \h]). Taken as a whole, the majority of the Group 1 studies imply that neurodevelopmental impacts due to altered maternal fT4 levels or presence of maternal hypothyroxinemia occur. In addition, the Group 2 studies (along with several Group 1 studies) also demonstrate adverse impact of maternal hypothyroxinemia on neurodevelopmental outcomes of the offspring. Overall, the results of this literature review lend support to the concept that maternal fT4, especially in the hypothyroxinemic range, is critical to the offspring's proper neurodevelopment. Across different age ranges and neurodevelopment indices, the impact of altered fT4 is seen even with small incremental changes in fT4 (and in populations with fT4 across the "normal" range). Further information on Group 1 and Group 2 studies that examined associations of thyroid hormone/hypothyroxinemia is detailed in Appendix I and is organized by neurodevelopmental endpoint.

In subsequent sections, two approaches are presented to link perchlorate doses to alterations in neurodevelopment, via alterations in thyroid hormone levels. Section [REF _Ref456208917 \r \h] presents the approach to connect changes in fT4 with changes in neurodevelopment as estimated by the five Group 1 studies identified as including data that could be used to quantitatively describe the relationship between thyroid hormone levels in early pregnancy and changes in neurodevelopment in offspring. Section [REF _Ref481160968 \r \h] presents an alternative option using the BBDR model to evaluate a shift in the proportion of the population that will fall below a hypothyroxinemic cut point, given exposure to perchlorate.

6. Informing the Derivation of an MCLG: Neurodevelopmental Effects

Based on the studies identified for additional quantitative analysis in Section [REF _Ref488161860 \n \h], this section presents potential approaches to connect perchlorate exposure and alterations in fT4 levels in pregnant women as predicted by the BBDR model to potential adverse neurodevelopmental impacts in the offspring. This section demonstrates how the EPA could inform the derivation of an MCLG for perchlorate by evaluating how various doses of perchlorate to a pregnant woman may result in changes in neurodevelopment of her child.

The BBDR model is capable of predicting fT4 levels at various gestational weeks of pregnancy for various iodine intake levels. For the purposes of this report, one gestational week was selected from each study of interest for analysis based on when fT4 values were collected. Given that none of the studies identified for additional quantitative analysis are specific to an iodine intake level, analyses were conducted to evaluate the impact of perchlorate on the potentially sensitive population of individuals with low iodine intake. That is, the analyses were conducted for individuals with an assumed iodine intake of 75 µg/day with pTSH = 0.398, as discussed in Section [REF _Ref482972870 \r \h]. Further, to evaluate the impact of fT4 at various percentiles, the EPA used the derived fT4 distributions (as described in Section [REF _Ref482787773 \r \h]) and calculated the resulting changes in the outcome of interest based on effect measures from the study of interest. Central, lower, and upper-bound effect estimates from the 95% CIs were used in all analyses.

An overview of the approach is presented in [REF _Ref482890788 \h]. While [REF _Ref482890788 \h] is specific for estimating neurodevelopmental effects for the low-iodine intake population, the same process could be followed for any iodine intake level that is output from the BBDR model. Analyses based on the results from each study are presented in alphabetical order.

Figure [SEQ Figure * ARABIC]. Outline of Approach to Assess the Effect of Doses of Perchlorate on Potential Neurodevelopmental Outcomes

[EMBED Visio.Drawing.15]

6.1 Analysis Using Endendijk et al. (2017)

As described in Section [REF _Ref512610865 \r \h], Endendijk et al. (2017) found an association between maternal fT4 in the first trimester and anxiety/depression. The authors reported an effect estimate of 0.12 (SE = 0.005) when controlling for maternal pre-natal psychopathology symptoms and TPO Ab in a linear regression analysis. Through personal communication with the author, the EPA determined that the anxiety/depression scores were inverse-transformed[23] in the model, and subsequently the relationship between fT4 and anxiety/depression can be described as:

$$\Delta AD = \left(\frac{1}{\beta * fT4_2}\right) - \left(\frac{1}{\beta * fT4_1}\right)$$

Where,

ΔAD = the change in the anxiety/depression score

β = 0.12 (95% CI: 0.11, 0.13)

$fT4_1$= fT4 concentration with no perchlorate dose

$fT4_2$= fT4 with increased dose of perchlorate

This function was used to evaluate how incremental changes in first-trimester fT4 output by the BBDR model impact an individual's anxiety/depression score as measured by the CBCL. To evaluate the impact of changes in fT4 levels due to perchlorate on anxiety/depression using the function estimated in Endendijk et al. (2017), GW 12 fT4 output from the BBDR model was used (see Section [REF _Ref482972870 \r \h]). Estimated fT4 levels at various percentiles were also used (see Section [REF _Ref485386250 \r \h]). GW 12 was selected because this was the week during the first trimester that fT4 measurements were taken from pregnant women in the Endendijk et al. (2017) study.

Results of an analysis demonstrating changes in anxiety/depression score as a result of increasing perchlorate doses are presented in [REF _Ref512612375 \h].

[23] The EPA has made an assumption that by inverse-transform, the authors meant that they used the reciprocal of each anxiety/depression score as the dependent variable in their models. The Agency has reached out to the study authors to confirm this assumption.

Table [SEQ Table * ARABIC]. Estimated Change in Anxiety/Depression Score Based on Endendijk et al. (2017) Central, Lower, and Upper Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ AD Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ AD Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ AD Central (Lower, Upper)[a]
Iodine Intake = 170 µg/day						
0	6.72	N/A	8.09	N/A	10.67	N/A
Iodine Intake = 75 µg/day						
0	5.58	N/A	6.71	N/A	8.85	N/A
1	5.51	0.02 (0.02, 0.02)	6.64	0.01 (0.01, 0.01)	8.78	0.01 (0.01, 0.01)
2	5.44	0.04 (0.04, 0.04)	6.57	0.03 (0.02, 0.03)	8.71	0.01 (0.01, 0.02)
3	5.38	0.06 (0.05, 0.06)	6.51	0.04 (0.04, 0.04)	8.65	0.02 (0.02, 0.02)
4	5.32	0.07 (0.07, 0.08)	6.45	0.05 (0.05, 0.06)	8.59	0.03 (0.03, 0.03)
5	5.26	0.09 (0.08, 0.10)	6.39	0.06 (0.06, 0.07)	8.53	0.04 (0.03, 0.04)
10	5.00	0.17 (0.16, 0.19)	6.13	0.12 (0.11, 0.13)	8.27	0.07 (0.06, 0.07)

[a] Result based on central, lower, and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.2 Analysis Using Finken et al. (2013)

As described in Section [REF _Ref485383673 \r \h * MERGEFORMAT], Finken et al. (2013) found an association between decreased fT4 levels and increased standard deviation of reaction time. This association, according to Finken et al. (2013) "…has been found to be related more strongly to individual difference in intelligence, cognitive aging, and neurological disorders" (Finken et al., 2013, p. 1419). This relationship was described in [REF _Ref457841191 \h * MERGEFORMAT], from Finken et al.'s (2013) multivariate regression analysis, which found that for every pmol/L decrease in fT4 there is a subsequent increase in the SD of reaction time with β = -4.9 (-9.5; -0.2), holding all else equal. This function was derived from and is thus applicable to the entire range of fT4 values in Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>]. It is unclear exactly what the entire range

encompasses, but the 2.5th percentile is reported as 6.5 pmol/L, and the interquartile range presented in the paper is 8.7 to 10.5 pmol/L.

Using the predicted changes in fT4 for increasing doses of perchlorate output by the BBDR model and estimating different distributional baselines, the following function can be used to estimate changes in the SD of reaction time as associated with changes in fT4:

$$\Delta\text{SD Reaction Time (ms)} = \beta \times \Delta\ \text{fT4}$$

Where:

β = -4.9 (95% CI: -9.5, -0.2)

Δ fT4 = $fT4_{increasedClO4} - fT4_{baselineClO4}$

To evaluate the impact of changes in fT4 levels due to perchlorate on the SD of reaction time using the function estimated in Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>], gestational week 13 fT4 output from the BBDR model was used (see Section [REF _Ref482972870 \r \h]). Estimated fT4 levels at various percentiles were also used (see Section [REF _Ref485386250 \r \h]). Gestational week 13 was selected because the median week of fT4 collection in the Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>] study was 12.9 (IQR: 11.9–14.3).

Results of an analysis demonstrating how increasing perchlorate dosage increases the SD of reaction time are presented in [REF _Ref485385829 \h].

Table [SEQ Table * ARABIC]. Estimated Change in the Standard Deviation of Reaction Time (milliseconds) based on Finken et al. (2013) Central, Lower, and Upper Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ RTSD Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ RTSD Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ RTSD Central (Lower, Upper)[a]
Iodine Intake = 170 µg/day						
0	6.70	N/A	8.07	N/A	10.64	N/A
Iodine Intake = 75 µg/day						
0	5.57	N/A	6.70	N/A	8.84	N/A
1	5.50	0.34 (0.01, 0.66)	6.63	0.34 (0.01, 0.66)	8.77	0.34 (0.01, 0.66)
2	5.43	0.67 (0.03, 1.30)	6.56	0.67 (0.03, 1.30)	8.71	0.67 (0.03, 1.30)
3	5.37	0.98 (0.04, 1.90)	6.50	0.98 (0.04, 1.90)	8.64	0.98 (0.04, 1.90)
4	5.31	1.28 (0.05, 2.48)	6.44	1.28 (0.05, 2.48)	8.58	1.28 (0.05, 2.48)
5	5.25	1.56 (0.06, 3.03)	6.38	1.56 (0.06, 3.03)	8.52	1.56 (0.06, 3.03)
10	4.99	2.83 (0.12, 5.48)	6.12	2.83 (0.12, 5.48)	8.27	2.83 (0.12, 5.48)

RTSD = Standard deviation of reaction time.
[a] Result based on central, lower, and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.3 Analysis Using Korevaar et al. (2016) and an EPA Analysis of Korevaar et al. (2016)

As summarized in Section [REF _Ref482388672 \r \h], Korevaar et al. (2016) presented a spline model and a multivariate regression with a quadratic term ([REF _Ref479341381 \h]) to explain the relationship between maternal fT4 and child IQ, both of which they found to have an inverted U-shaped association. Korevaar provided the EPA with complete study data,[24] and subsequently the EPA confirmed the authors' conclusion that the regression analysis with the quadratic term sufficiently explained the relationship between maternal fT4 and child IQ assessed with the spline model.

6.3.1 Analysis with Quadratic Function from Korevaar et al. (2016)

Given the adequate fit of the quadratic regression model, the EPA used the quadratic equation coefficients put forth in [REF _Ref479341381 \h] to determine the changes in child IQ for given changes in maternal fT4. The following function was used to determine the change in child IQ for a given change in maternal fT4 due to perchlorate:

$$\Delta IQ = (\beta_1 \times lnfT4_2 + \beta_2 \times ln(fT4_2)^2) - (\beta_1 \times lnfT4_1 + \beta_2 \times ln(fT4_1)^2)$$

Where:

[24] Data were provided by Dr. Tim Korevaar on February 6, 2017.

β_1 = 33.81 (95% CI: 9.8, 57.82)

β_2 = -6.235 (95% CI: -10.567, -1.903)

$fT4_1$ = fT4 when perchlorate dose = 0 µg/kg/day at a given fT4 percentile for the low-iodine intake population.

$fT4_2$ = fT4 when perchlorate dose is at a defined dose, X, which is greater than 0 µg/kg/day, for the low-iodine intake population.

To evaluate the impact of perchlorate induced changes in fT4 levels on IQ using the estimated function from Korevaar et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Korevaar</Author><Year>2016</Year><RecNum>313</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>313</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832236">313</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, Tim I. M.</author><author>Muetzel, Ryan</author><author>Medici, Marco</author><author>Chaker, Layal</author><author>Jaddoe, Vincent W. V.</author><author>de Rijke, Yolanda B.</author><author>Steegers, Eric A. P.</author><author>Visser, Theo J.</author><author>White, Tonya</author><author>Tiemeier, Henning</author><author>Peeters, Robin P.</author></authors></contributors><titles><title>Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study</title><secondary-title>The Lancet Diabetes & Endocrinology</secondary-title></titles><periodical><full-title>The Lancet Diabetes & Endocrinology</full-title></periodical><pages>35-43</pages><volume>4</volume><number>1</number><dates><year>2016</year></dates><isbn>22138587</isbn><urls></urls><electronic-resource-num>10.1016/s2213-8587(15)00327-7</electronic-resource-num></record></Cite></EndNote>], GW 13 fT4 output from the BBDR model was used (see Section [REF _Ref482972870 \r \h]), along with the estimated fT4 levels at various percentiles (see Section [REF _Ref485386250 \r \h]). Gestational week 13 was selected because the median week of fT4 collection in this study was 13.2 weeks (range 9–18 GW). The results of this analysis are presented in [REF _Ref490658761 \h].

Table [SEQ Table * ARABIC]. Estimated Change in Nonverbal IQ, based on Korevaar et al. (2016) Central, Lower, and Upper Quadratic-Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[a]
Iodine Intake = 170 µg/day						
0	6.70	N/A	8.07	N/A	10.64	N/A
Iodine Intake = 75 µg/day						
0	5.57	N/A	6.70	N/A	8.84	N/A
1	5.50	-0.16 (0.33, -0.65)	6.63	-0.11 (0.32, -0.53)	8.77	-0.05 (0.29, -0.39)
2	5.43	-0.31 (0.65, -1.27)	6.56	-0.21 (0.62, -1.04)	8.71	-0.10 (0.56, -0.77)
3	5.37	-0.46 (0.95, -1.88)	6.50	-0.31 (0.91, -1.53)	8.64	-0.15 (0.82, -1.13)
4	5.31	-0.61 (1.25, -2.46)	6.44	-0.41 (1.19, -2.01)	8.58	-0.20 (1.08, -1.48)
5	5.25	-0.75 (1.52, -3.03)	6.38	-0.51 (1.46, -2.47)	8.52	-0.25 (1.32, -1.82)
10	4.99	-1.43 (2.77, -5.63)	6.12	-0.96 (2.65, -4.57)	8.27	-0.48 (2.40, -3.35)

[1] Result based on central, lower and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.3.2 EPA Independent Analysis of Korevaar et al. (2016) Data

The EPA conducted an additional analysis of the Korevaar et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Korevaar</Author><Year>2016</Year><RecNum>313</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>313</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832236">313</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, Tim I. M.</author><author>Muetzel, Ryan</author><author>Medici, Marco</author><author>Chaker, Layal</author><author>Jaddoe, Vincent W. V.</author><author>de Rijke, Yolanda B.</author><author>Steegers, Eric A. P.</author><author>Visser, Theo J.</author><author>White, Tonya</author><author>Tiemeier, Henning</author><author>Peeters, Robin P.</author></authors></contributors><titles><title>Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study</title><secondary-title>The Lancet Diabetes & Endocrinology</secondary-title></titles><periodical><full-title>The Lancet Diabetes & Endocrinology</full-title></periodical><pages>35-43</pages><volume>4</volume><number>1</number><dates><year>2016</year></dates><isbn>22138587</isbn><urls></urls><electronic-resource-num>10.1016/s2213-8587(15)00327-7</electronic-resource-num></record></Cite></EndNote>] data to account for uncertainties related to the original Korevaar et al. (2016) analysis. The study authors agreed to share their original dataset, and the EPA was thus able to further refine the model relating maternal fT4 and child IQ.

The first step in this reanalysis was to develop a causal model for the effect of maternal fT4 and child IQ in order to identify the minimum set of confounders. The EPA accomplished this by examining the literature for documented causal relationships between each of the variables that were originally

included in the Korevaar et al. (2016) model. This process allowed for the identification of the minimum set of variables that adequately controlled for confounding of the relationship between maternal fT4 and child IQ.

Identification of Proper Functional Form

After identifying the minimum set of confounders, the EPA tested models using ln(fT4) as the independent variable, as well as using raw, untransformed fT4 as the independent variable of interest. Three different functional forms were tested: a cubic restricted spline as was used in the original Korevaar et al. (2016) manuscript, a quadratic equation as was also estimated in the original Korevaar et al. (2016) manuscript, and a linear spline model. The linear spline form would allow for the use of a spline function with a more straightforward estimation of betas over the range of the function than the cubic restricted spline. The EPA opted to use the same knots in the spline functions that the study authors used in the original manuscript for both the linear and the cubic restricted splines: the 10^{th} percentile, the 50^{th} percentile, and the 90^{th} percentile. Overall, six models using the minimum set of confounders would be estimated, three using ln(fT4) as the independent variable, and three using raw fT4 as the independent variable. The cubic restricted spline models and the linear spline models were estimated using the "mkspline" command in Stata [ADDIN EN.CITE <EndNote><Cite><Author>StataCorp</Author><Year>2015</Year><RecNum>1984</RecNum><DisplayText>(StataCorp, 2015)</DisplayText><record><rec-number>1984</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1524593247">1984</key></foreign-keys><ref-type name="Computer Program">9</ref-type><contributors><authors><author>StataCorp</author></authors></contributors><titles><title>Stata Statistical Software: Release 14</title></titles><dates><year>2015</year></dates><pub-location>College Station, TX</pub-location><publisher>StataCorp LP</publisher><urls></urls></record></Cite></EndNote>]. The "mkspline" syntax used for each model is reported in Appendix J.

Additional Adjustments to the Analysis Sample

It was determined that there were many values of the independent variable of interest, fT4, which were imputed using multiple imputation by the study authors. The EPA opted to drop all data points that did not have a measured value for fT4 in the original data to avoid impacting the estimation of the effect estimate of the independent variable of interest with data that were not directly measured. However, the EPA continued to use the multiply imputed dataset for all other variables. The EPA also decided *a priori* to drop a single data point with an fT4 value above 90 pmol/L, as it was suspected that this value had a large influence on the estimation of the EPA's models, and may have been an invalid data point.

Choosing a Preferred Model

The causal model building process identified two minimum sets of confounders that would effectively isolate the total effect of maternal fT4 on child IQ. The first set includes:

- Continuous maternal age in years;
- Categorical maternal smoking status (non-smoker, previous smoker, or current smoker); and

- Categorical maternal ethnicity (Dutch, Moroccan, Turkish, Surinamese, Cape Verdian, Dutch Antilles, Indonesian, Asian, "other European, North American, or Australian," or "other Asian, African, or South American").

The second set of confounding variables includes:

- Categorical maternal education (none or primary only, secondary phase (3-4 years), secondary phase (4-5 years), higher phase 1 (6-8 years), or higher phase 2 (>8 years));
- Categorical maternal smoking status (previously defined); and
- Categorical maternal ethnicity (previously defined.)

The EPA moved forward with models utilizing both of these minimum sets of confounders, and opted to use model fit statistics to eventually choose the most appropriate set.

Since there were two minimum sets of confounders identified by the EPA's causal model, 12 models were estimated in total (six for each minimum set of confounders). Each model was estimated as previously described, and beta estimates were compared for effect plausibility, as were overall model fit estimates using adjusted R^2 statistics and F-statistics. Since the data were multiply imputed, adjusted R^2 statistics were calculated as the mean adjusted R^2 statistic when estimating the model on each multiply imputed dataset separately. This was done using the "mibeta" command in Stata [ADDIN EN.CITE <EndNote><Cite><Author>StataCorp</Author><Year>2015</Year><RecNum>1984</RecNum><DisplayText>(StataCorp, 2015)</DisplayText><record><rec-number>1984</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1524593247">1984</key></foreign-keys><ref-type name="Computer Program">9</ref-type><contributors><authors><author>StataCorp</author></authors></contributors><titles><title>Stata Statistical Software: Release 14</title></titles><dates><year>2015</year></dates><pub-location>College Station, TX</pub-location><publisher>StataCorp LP</publisher><urls></urls></record></Cite></EndNote>]. Adjusted R^2 statistics and F-statistics for each model are presented in [REF _Ref512353025 \h].

Table [SEQ Table * ARABIC]. Adjusted R^2 Statistics and F-Statistics for Each Estimated Model

Model Specification	Adjusted R^2	F-Statistic (Model DF, Residual DF)
Controlling for age, smoking, ethnicity		
Linear spline; untransformed fT4	0.102	25.98 (16, 3512.2)
Linear spline; natural log fT4	0.102	26.06 (16, 3513.1)
Cubic restricted spline; untransformed fT4	0.101	29.37 (14, 3473.8)

Model Specification	Adjusted R^2	*F*-Statistic (Model DF, Residual DF)
Cubic restricted spline; natural log fT4	0.102	29.49 (14, 3472.4)
Quadratic; untransformed fT4	0.099	28.65 (14, 3480.8)
Quadratic; natural log fT4	0.101	29.23 (14, 3478.7)
Controlling for education, smoking, ethnicity		
Linear spline; untransformed fT4	0.132	28.53 (19, 3285.2)
Linear spline; natural log fT4	0.132	28.60 (19, 3285.2)
Cubic restricted spline; untransformed fT4	0.131	31.49 (17, 3188.1)
Cubic restricted spline; natural log fT4	0.132	31.64 (17, 3186.0)
Quadratic; untransformed fT4	0.129	31.05 (17, 3201.5)
Quadratic; natural log fT4	0.131	31.42 (17, 3190.5)

By comparing adjusted R^2 statistics, the minimum set of confounders was determined for which the set that included mother's education, smoking status, and mother's ethnicity had a superior fit than with the other minimum set, regardless of the functional form utilized for the model. The EPA moved forward using this minimum set of confounders only. The Agency also determined that the linear spline function had the highest adjusted R^2 value among the different functional forms. This form was preferred *a priori* as it was more flexible than the quadratic equation, and also easier to estimate betas from than the cubic restricted spline for use in a concentration-response function. Although the cubic restricted spline models had a slightly higher F-statistic than the linear spline models, the EPA chose to move forward with the linear spline models, as the improvement in fit was not large enough to warrant the much greater complexity of using the cubic restricted spline models for predictive modeling. The choice between the use of ln(fT4) and untransformed fT4 was difficult, as each function had a very similar adjusted R^2 value, although the function utilizing ln(fT4) had a marginally higher adjusted R^2. The EPA chose to assess the model assumptions for both ln(fT4) and untransformed fT4 using the linear spline function that controlled for education, smoking status, and mother's ethnicity.

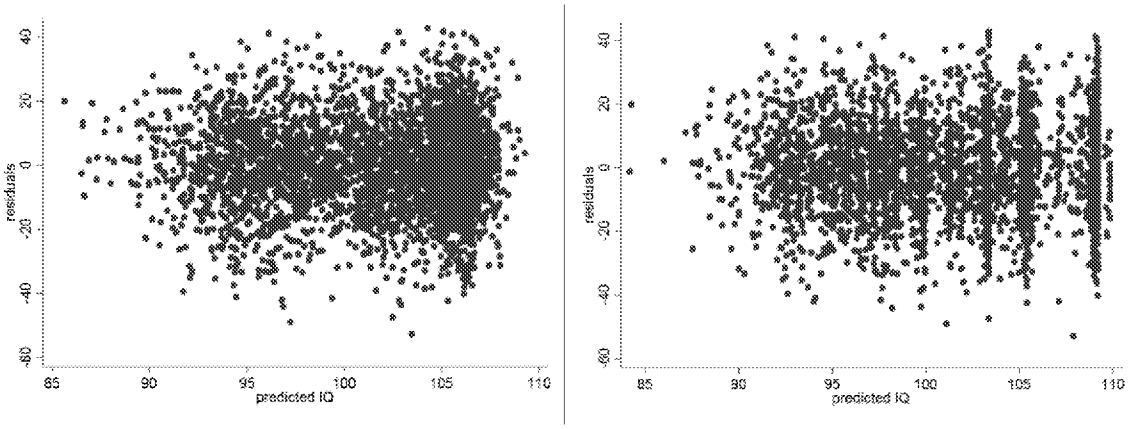
The EPA also tested models that included an interaction term between gestational age at blood draw and ln(fT4) (or fT4), given the natural variability of fT4 throughout the course of pregnancy, and thus the changing definition of low or high fT4 by gestational week. The fit of these models was similar to those models without the interaction term presented above, but the F-statistics of the models were

substantially lower due to the increased model degrees of freedom from the increased number of variables included in the model. The results of this analysis are presented in Appendix J.

Post Hoc Model Assumption Tests

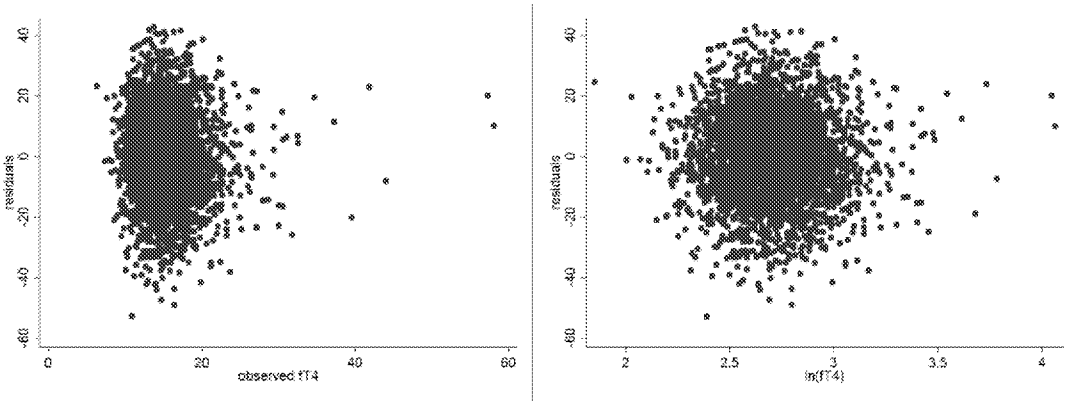
After estimating these two linear spline functions, residuals were examined for patterns that would violate the assumptions of the regression models. Neither model displayed convincing evidence of a relationship between residuals and model predicted values; however, there was some evidence of heteroscedasticity between residuals and the EPA's independent variable of interest. Scatterplots examining these potential assumption violations are presented in [REF _Ref512353059 \h] and [REF _Ref512353068 \h].

Figure [SEQ Figure * ARABIC]. Plots of Model Residuals versus Predicted IQ for Both Linear Spline Models



Note: Model using untransformed fT4 on left, model using natural log fT4 on right.

Figure [SEQ Figure * ARABIC]. Plots of Model Residuals versus fT4 and Natural Log fT4 for Both Linear Spline Models



Note: Model using untransformed fT4 on left, model using natural log fT4 on right.

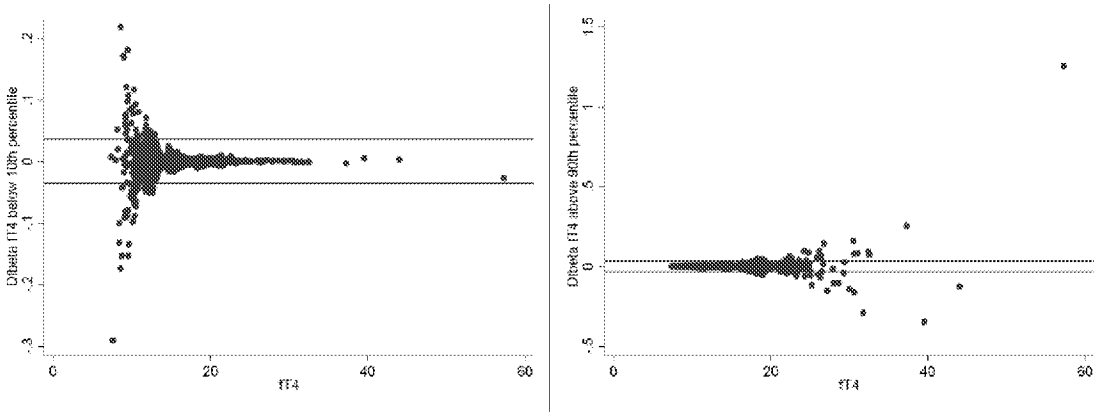
To test for heteroscedasticity in its models, the EPA ran the Breusch-Pagan and the Cook-Weisberg tests [ADDIN EN.CITE <EndNote><Cite><Author>Breusch</Author><Year>1979</Year><RecNum>1981</RecNum><Di

splayText>(Breusch & Pagan, 1979; Cook & Weisberg, 1983)</DisplayText><record><rec-number>1981</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1524592792">1981</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Breusch, T. S.</author><author>Pagan, A. R.</author></authors></contributors><titles><title>A simple test for heteroscedasticity and random coefficient variation</title><secondary-title>Econometrica</secondary-title></titles><periodical><full-title>Econometrica</full-title></periodical><pages>1287</pages><volume>47</volume><number>5</number><dates><year>1979</year></dates><isbn>00129682</isbn><urls><related-urls><url><style face="underline" font="default" size="100%">https://www.jstor.org/stable/1911963?origin=crossref</style></url></related-urls></urls><electronic-resource-num>10.2307/1911963</electronic-resource-num><language>en</language><access-date>2018-04-13 15:39:41</access-date></record></Cite><Cite><Author>Cook</Author><Year>1983</Year><RecNum>1982</RecNum><record><rec-number>1982</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1524592933">1982</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Cook, R. Dennis</author><author>Weisberg, Sanford</author></authors></contributors><titles><title>Diagnostics for heteroscedasticity in regression</title><secondary-title>Biometrika</secondary-title></titles><periodical><full-title>Biometrika</full-title></periodical><pages>1-10</pages><volume>70</volume><number>1</number><dates><year>1983</year></dates><isbn>0006-3444</isbn><urls></urls><electronic-resource-num>10.1093/biomet/70.1.1</electronic-resource-num><language>English (US)</language></record></Cite></EndNote>], as well as White's general test for heteroscedasticity [ADDIN EN.CITE <EndNote><Cite><Author>White</Author><Year>1980</Year><RecNum>1980</RecNum><DisplayText>(White, 1980)</DisplayText><record><rec-number>1980</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1524592668">1980</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>White, Halbert</author></authors></contributors><titles><title>A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity</title><secondary-title>Econometrica</secondary-title></titles><periodical><full-title>Econometrica</full-title></periodical><pages>817–838</pages><volume>48</volume><number>4</number><dates><year>1980</year></dates><isbn>00129682, 14680262</isbn><urls><related-urls><url><style face="underline" font="default" size="100%">http://www.jstor.org/stable/1912934</style></url></related-urls></urls></record></Cite></EndNote>]. None of these tests suggested evidence of heteroscedasticity, and thus it was concluded that the models conformed to the regression assumption of homoscedastic residuals.

The EPA also tested the estimated models for influential observations using the DFBETA technique to see how much influence each data point had on effect estimates. DFBETA essentially removes each point one at a time from the regression analysis and measures the effect removing the point has on each beta estimate. A "rule of thumb" is that a point that affects betas by more than 2/sqrt(n) is worth investigating further. DFBETA plots for the estimated beta for fT4 values below the 10th

percentile, as well as for the estimated beta for fT4 values above the 90th percentile, are shown in [REF _Ref512353091 \h].

Figure [SEQ Figure * ARABIC]. Plots of DFBETAs versus fT4 for Estimated Beta Representing fT4 Values below the 10th Percentile and Estimated Beta Representing fT4 Values above the 90th Percentile



Note: Beta for fT4 values under 10th percentile on left, beta for fT4 values above 90th percentile on right. Red lines represent +/- 2/sqrt(n) for this model, or +/- 0.36.

From these analyses, the EPA opted to drop one data point because of its strong influence on regression betas ([REF _Ref512353091 \h] and [REF _Ref512353166 \h]). This data point had a very high fT4 value, coupled with a high IQ value. The data point is represented by the outlier on the right scatter plot in [REF _Ref512353091 \h]. The IQ and fT4 values of the omitted data point are shown in [REF _Ref512353166 \h].

Table [SEQ Table * ARABIC]. Data Point Dropped from Analysis due to Large Influence on Results

Data point	fT4 (pmol/L)	IQ
1	57.318	119

Model results including this influential data point are included in Appendix J.

Final Model Results

Once this data point was removed, the two linear spline models were re-estimated. The betas, adjusted R^2 statistics, and F-statistics are reported in [REF _Ref512353213 \h].

Table [SEQ Table * ARABIC]. Model Results, Adjusted R^2 and *F*-Statistics

Model Specification	Child IQ β (95% CI)	P-Value	Adjusted R^2	F-Statistic (Model DF, Residual DF)
Untransformed fT4				
Beta below 10th percentile fT4	1.73 (0.44, 3.02)*	0.009	0.132	28.58 (19, 3281.1)
Beta between 10th and 50th percentile fT4	-0.02 (-0.60, -0.56)	0.944		
Beta between 50th and 90th percentile fT4	-0.09 (-0.50, 0.32)	0.658		
Beta above 90th percentile fT4	-0.37 (-0.70, -0.03)*	0.033		
Log-transformed fT4				
Beta below 10th percentile ln(fT4)	17.26 (3.77, 30.75)*	0.012	0.132	28.64 (19, 3282.2)
Beta between 10th and 50th percentile ln(fT4)	-0.16 (-7.91, 7.59)	0.968		
Beta between 50th and 90th percentile ln(fT4)	-0.61 (-7.57, 6.35)	0.863		
Beta above 90th percentile ln(fT4)	-10.98 (-19.69, -2.26)*	0.014		

Note: 10th percentile fT4 = 11.77 pmol/L. 50th percentile fT4 = 14.76 pmol/L. 90th percentile fT4 = 18.94 pmol/L. 10th percentile log-transformed fT4 = 2.47. 50th percentile log-transformed fT4 = 2.69. 90th percentile log-transformed fT4 = 2.94. * signifies beta estimates statistically significant at the 95% confidence level.

Given the slightly better fit of the log-transformed fT4 model, the EPA designated this model as the preferred model. Using the predicted changes in fT4 for increasing doses of perchlorate from the BBDR model, the following function can be used to estimate changes in IQ as a result of changes in fT4:

When $fT4_1$ and $fT4_2$ are both less than or equal to 11.76[25] pmol/L:

$$\Delta IQ = (\beta_1 \times \ln(fT4_2)) - (\beta_1 \times \ln(fT4_1))$$

Where:

β_1 = 17.26 (3.77, 30.75)

$fT4_1$ = fT4 when perchlorate dose = 0 µg/kg/day at a given fT4 percentile

$fT4_2$ = fT4 when perchlorate dose is at a defined dose, X, which is greater than 0 µg/kg/day

Note that when the fT4 values are greater than 11.76 the function and beta effect estimates will vary. However, given that the BBDR model results estimate the median fT4 to be 10.7 pmol/L with adequate iodine (i.e., iodine intake = 170 µg/day), using different effect estimates is unlikely.

Results of an analysis demonstrating how increasing perchlorate dosage decreases IQ based on the EPA's analysis of the Korevaar et al. (2016) data are presented in [REF _Ref485387377 \h] using the beta estimates reported in [REF _Ref512353213 \h].

[25] This and the other fT4 values presented in this key for the above function represent untransformed values of the ln(fT4) values at each knot of the spline. The values were obtained by calculating exp(ln(fT4)).

Table [SEQ Table * ARABIC]. Estimated Change in IQ, Based on Independent Analysis of Korevaar et al. (2016) Central, Lower, and Upper Multivariate-Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ IQ Central (Lower, Upper)[a]
Iodine Intake = 170 µg/day						
0	6.70	N/A	8.07	N/A	10.64	N/A
Iodine Intake = 75 µg/day						
0	5.57	N/A	6.70	N/A	8.84	N/A
1	5.50	-0.22 (-0.05, -0.39)	6.63	-0.18 (-0.04, -0.32)	8.77	-0.14 (-0.03, -0.24)
2	5.43	-0.43 (-0.09, -0.76)	6.56	-0.36 (-0.08, -0.63)	8.71	-0.27 (-0.06, -0.48)
3	5.37	-0.63 (-0.14, -1.12)	6.50	-0.52 (-0.11, -0.93)	8.64	-0.39 (-0.09, -0.70)
4	5.31	-0.83 (-0.18, -1.47)	6.44	-0.68 (-0.15, -1.22)	8.58	-0.52 (-0.11, -0.92)
5	5.25	-1.02 (-0.22, -1.81)	6.38	-0.84 (-0.18, -1.50)	8.52	-0.63 (-0.14, -1.13)
10	4.99	-1.89 (-0.41, -3.36)	6.12	-1.55 (-0.34, -2.77)	8.27	-1.16 (-0.25, -2.07)

[a] Result based on central, lower, and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.4 Analysis using Pop et al. (1999, 2003)

As summarized in Section [REF _Ref482388672 \r \h], two Pop et al. papers found a relationship between fT4 and neurodevelopmental outcomes measured using the BSID. Specifically, Pop et al. (1999, 2003) found a relationship between changes in fT4 and PDI. Pop et al. (2003) also found a relationship between fT4 and MDI. Using the WebPlotDigitizer Extension for Google Chrome and using the linear regression function in Excel (2013), effect estimates were estimated based on a bivariate linear regression analysis. The effect estimates and their associated 95% CIs are summarized in [REF _Ref485388464 \h].

Table [SEQ Table * ARABIC]. Pop et al. (1999, 2003) Effect Estimates[a]

Study/Endpoint	β (95% CI)
Pop et al. (1999)/PDI	8.5 (95% CI: 0.01, 17.0)
Pop et al. (2003)/PDI	8.4 (95% CI: 4.0, 12.8)
Pop et al. (2003)/MDI	6.3 (95% CI: 1.9, 10.6)

[a] All estimates are based on bivariate regression analysis of digitized data.

These Pop et al. (1999, 2003) functions are specific to the individuals in their sample who were hypothyroxinemic. In Pop et al. (1999) the 10th percentile hypothyroxinemic cut point corresponded to an fT4 level of 10.4 pmol/L, and in Pop et al. (2003) this corresponded to an fT4 level of 12.4 pmol/L. The 10.4 pmol/L level is between the 43rd and 44th percentile of the median iodine intake and between the 87th and the 88th percentile of the 75 µg/day iodine intake distributions predicted by the BBDR model and estimated distribution as explained in Section [REF _Ref482274870 \r \h]. The lowest fT4 level evaluated in Pop et al. (1999) was 7.86 pmol/L[26]. The 12.4 pmol/L level is equivalent to between the 84th and 85th percentile of the median iodine intake and between the 99th and 99.5th percentile of the 75 µg/day iodine intake distributions predicted by the BBDR model and estimated distribution as explained in Section [REF _Ref482274870 \r \h]. The lowest fT4 level evaluated in Pop et al. (2003) was 8.39 pmol/L.[NOTEREF _Ref488142491 \h * MERGEFORMAT]

To evaluate the impact of the changes in fT4 levels due to perchlorate on MDI and PDI using the Pop et al. (1999, 2003) studies, the EPA used GW 12 fT4 output from the BBDR model (see Section [REF _Ref482972870 \r \h]), along with the estimated fT4 levels at various percentiles (see Section [REF _Ref485386250 \r \h]). This is because Pop et al. (1999, 2003) measured fT4 levels in their study populations at GW 12. The subsequent subsections outline the specific analysis and results for each study/endpoint combination from the Pop et al. (1999, 2003) analyses.

6.4.1 Analysis for Pop et al. (1999) – PDI

To evaluate the impact that a change in fT4 as a result of an increased dose of perchlorate will have on resulting PDI scores based on Pop et al. (1999), the following equation was utilized:

$$\Delta PDI = \beta \times \Delta fT4 \ (fT4 \text{ in pmol/L})$$

Where:

β = 8.5 (95% CI: 0.01, 17.0)

Δ fT4 = $fT4_{increasedClO4} - fT4_{baselineClO4}$

Results of an analysis demonstrating how increasing perchlorate dosage decreases PDI based on Pop et al. (1999) are presented in [REF _Ref485389086 \h].

[26] This value was extracted from the digitized datasets from the Pop et al. (1999, 2003) analyses.

Table [SEQ Table * ARABIC]. Estimated Change in PDI, Based on Pop et al. (1999) Central, Lower, and Upper Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[a]
Iodine Intake = 170 µg/day						
0	6.72	N/A	8.09	N/A	10.67	N/A
Iodine Intake = 75 µg/day						
0	5.58	N/A	6.71	N/A	8.85	N/A
1	5.51	-0.60 (0.00, -1.21)	6.64	-0.60 (0.00, -1.21)	8.78	-0.60 (0.00, -1.21)
2	5.44	-1.17 (0.00, -2.35)	6.57	-1.17 (0.00, -2.35)	8.71	-1.17 (0.00, -2.35)
3	5.38	-1.72 (0.00, -3.44)	6.51	-1.72 (0.00, -3.44)	8.65	-1.72 (0.00, -3.44)
4	5.32	-2.24 (0.00, -4.48)	6.45	-2.24 (0.00, -4.48)	8.59	-2.24 (0.00, -4.48)
5	5.26	-2.74 (0.00, -5.47)	6.39	-2.74 (0.00, -5.47)	8.53	-2.74 (0.00, -5.47)
10	5.00	-4.94 (-0.01, -9.88)	6.13	-4.94 (-0.01, -9.88)	8.27	-4.94 (-0.01, -9.88)

[a] Result based on central, lower, and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.4.2 Analysis for Pop et al. (2003) – PDI

To evaluate the impact that a change in fT4 as a result of an increased dose of perchlorate will have on resulting PDI scores based on Pop et al. (2003), the following equation was utilized:

$$\Delta PDI = \beta \times \Delta fT4 \ (fT4 \text{ in pmol/L})$$

Where:

β = 8.4 (95% CI: 4.0, 12.8)

Δ fT4 = $fT4_{increasedClO4} - fT4_{baselineClO4}$

Results of an analysis demonstrating how increasing perchlorate dosage decreases PDI based on Pop et al. (2003) are presented in [REF _Ref485389400 \h].

Table [SEQ Table * ARABIC]. Estimated Change in PDI, Based on Pop et al. (2003) Central, Lower, and Upper Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ PDI Central (Lower, Upper)[a]
Iodine Intake = 170 µg/day						
0	6.72	N/A	8.09	N/A	10.67	N/A
Iodine Intake = 75 µg/day						
0	5.58	N/A	6.71	N/A	8.85	N/A
1	5.51	-0.60 (-0.28, -0.91)	6.64	-0.60 (-0.28, -0.91)	8.78	-0.60 (-0.28, -0.91)
2	5.44	-1.16 (-0.55, -1.77)	6.57	-1.16 (-0.55, -1.77)	8.71	-1.16 (-0.55, -1.77)
3	5.38	-1.70 (-0.81, -2.59)	6.51	-1.70 (-0.81, -2.59)	8.65	-1.70 (-0.81, -2.59)
4	5.32	-2.21 (-1.05, -3.37)	6.45	-2.21 (-1.05, -3.37)	8.59	-2.21 (-1.05, -3.37)
5	5.26	-2.70 (-1.29, -4.12)	6.39	-2.70 (-1.29, -4.12)	8.53	-2.70 (-1.29, -4.12)
10	5.00	-4.88 (-2.32, -7.44)	6.13	-4.88 (-2.32, -7.44)	8.27	-4.88 (-2.32, -7.44)

[a] Result based on central, lower, and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.4.3 Analysis for Pop et al. (2003) – MDI

To evaluate the impact that a change in fT4 as a result of an increased dose of perchlorate will have on resulting MDI scores based on Pop et al. (2003), the following equation was utilized:

$$\Delta MDI = \beta \times \Delta fT4 \ (fT4 \text{ in pmol/L})$$

Where:

β = 6.3 (95% CI: 1.92, 10.6)

Δ fT4 = $fT4_{increasedClO4} - fT4_{baselineClO4}$

Results of an analysis demonstrating how increasing perchlorate dosage decreases MDI based on Pop et al. (2003) are presented in [REF _Ref485389508 \h].

Table [SEQ Table * ARABIC]. Estimated Change in MDI, Based on Pop et al. (2003) Central, Lower, and Upper Beta Estimates due to a Change in Perchlorate Dose from 0 µg/kg/day at Various Percentiles of fT4

Dose of Perchlorate (µg/kg/day)	fT4 Percentile					
	2.5th		10th		50th	
	fT4 (pmol/L)	Δ MDI Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ MDI Central (Lower, Upper)[a]	fT4 (pmol/L)	Δ MDI Central (Lower, Upper)[a]
Iodine Intake = 170 µg/day						
0	6.72	N/A	8.09	N/A	10.67	N/A
Iodine Intake = 75 µg/day						
0	5.58	N/A	6.71	N/A	8.85	N/A
1	5.51	-0.45 (-0.14, -0.75)	6.64	-0.45 (-0.14, -0.75)	8.78	-0.45 (-0.14, -0.75)
2	5.44	-0.87 (-0.27, -1.46)	6.57	-0.87 (-0.27, -1.46)	8.71	-0.87 (-0.27, -1.46)
3	5.38	-1.27 (-0.39, -2.14)	6.51	-1.27 (-0.39, -2.14)	8.65	-1.27 (-0.39, -2.14)
4	5.32	-1.66 (-0.51, -2.79)	6.45	-1.66 (-0.51, -2.79)	8.59	-1.66 (-0.51, -2.79)
5	5.26	-2.03 (-0.62, -3.41)	6.39	-2.03 (-0.62, -3.41)	8.53	-2.03 (-0.62, -3.41)
10	5.00	-3.66 (-1.12, -6.16)	6.13	-3.66 (-1.12, -6.16)	8.27	-3.66 (-1.12, -6.16)

[a] Result based on central, lower, and upper 95% CI effect estimates; BBDR model output using pTSH = 0.398; calibrated for median population. Additional details can be found in Appendix A.

6.5 Uncertainties Related to the Approach

The approach presented in this report is dependent upon predictions from the BBDR model, the derivation of the distribution of fT4, and the evaluations of the relationship between fT4 and neurodevelopment. Each of these steps has inherent uncertainties associated with it. Uncertainties associated with the BBDR model and derivation of the distribution of fT4 have been discussed previously (see Sections [REF _Ref482965010 \r \h] and [REF _Ref482965013 \r \h], respectively). One global uncertainty in this analysis is that the state of the science on the relationship between maternal fT4 levels and offspring neurodevelopment is constantly evolving. For example, since the literature review for this report ceased, at least one additional article has been published evaluating the relationship between maternal fT4 and adverse neurodevelopmental outcomes [ADDIN EN.CITE ADDIN EN.CITE.DATA]. The impact of future research on this assessment is unknown.

This section will focus on the uncertainties related to the literature identified that connects the estimated maternal fT4 levels with offspring neurodevelopmental outcomes and the subsequent quantitative analysis. Specifically, the first sections (Section [REF _Ref492564492 \n \h] through [

REF _Ref492564536 \n \h]) discuss uncertainties as they pertain to attributes of the body of literature evaluating incremental changes in fT4 and their potential association with incremental changes in neurodevelopmental outcomes. Section [REF _Ref492583568 \r \h] discusses uncertainties related to the underlying quantitative analyses.

6.5.1 Population for Which Dose-Response Information Is Available

The SAB stated that fetuses of hypothyroxinemic women may be a potentially sensitive life stage (SAB, 2013). However, the majority of Group 1 studies presented analyses using the full range of maternal fT4 for the population to assess incremental changes as they relate to subsequent neurodevelopment of their offspring, compared to evaluating incremental changes in maternal fT4 only in the hypothyroxinemic range. This may help to explain why many of the studies identified in the literature review did not find a statistically significant relationship between continuous maternal fT4 and neurodevelopment. As demonstrated in Korevaar et al. (2016), there may be an ideal range of maternal fT4 values, and the greatest impact of change will occur when maternal fT4 values fall below or above that range. When comparing offspring of mothers who experienced hypothyroxinemia to offspring of those who did not, adverse neurodevelopmental outcomes were more consistently related to exposure to maternal hypothyroxinemia, compared to evaluating incremental changes in maternal fT4 across the full spectrum. Thus, uncertainty exists as to whether the studies evaluating the full spectrum of fT4 are underestimating the impact of fT4 on neurodevelopment for the sensitive population of the fetuses of hypothyroxinemic pregnant women.

Further, none of the current studies analyzed in Section [REF _Ref456208917 \r \h * MERGEFORMAT] are based on a U.S. population. The data from all papers are from the Netherlands and are being considered for use to inform the derivation of an MCLG for the United States. There is no reason to believe that the impact of fT4 on neurodevelopment would differ by country, unless there is a substantial difference in iodine intake. Unfortunately, exact data on iodine intake levels in the Pop et al. (1999, 2003) papers are not provided. However, the authors cite two studies on iodine levels in the general population of the Netherlands. Van Rees-Wortelboer et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>van Rees-Wortelboer</Author><Year>1987</Year><RecNum>298</RecNum><DisplayText>(1987)</DisplayText><record><rec-number>298</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1470950295">298</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>van Rees-Wortelboer, M. M., </author><author>Schröder-van der Elst, J. P., </author><author>Lycklama, A.,</author><author>Van der Heide, D. </author></authors></contributors><titles><title>Iodine and goiter in The Netherlands</title><secondary-title>Nederlands Tijdschrift voor Geneeskunde</secondary-title></titles><periodical><full-title>Nederlands Tijdschrift voor Geneeskunde</full-title></periodical><pages>1821-1824</pages><volume>121</volume><number>41</number><dates><year>1987</year></dates><urls></urls></record></Cite></EndNote>] studied a sample of 253 Dutch women aged 23–32 and found a mean urinary iodide excretion (corrected for creatinine) of 115 µg/g creatinine. Brussaard et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Brussaard</Author><Year>1997</Year><RecNum>55</RecNum><DisplayText>(1997)</DisplayText><record><rec-number>55</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437143470">55</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Brussaard, J H</author><author>Hulshof, K F</author><author>Kistemaker, C</author><author>Lowik, M R</author></authors></contributors><titles><title>Adequcy of the iodine supply in the Netherlands</title><secondary-title>European Journal of Clinical Nutrition</secondary-title></titles><periodical><full-title>European Journal of Clinical Nutrition</full-title></periodical><pages>5</pages><volume>51</volume><section>11</section><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>] compiled studies on iodine supply after the introduction of iodized salt in the Netherlands in 1982. The researchers found that estimates of the mean iodine intake in women under the age of 65 ranged from 135 to 149 µg/day. An additional study of Dutch food consumption data from 1997 to 1998 by Verkaik-Kloosterman et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Verkaik-Kloosterman</Author><Year>2010</Year><RecNum>299</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>299</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1470950359">299</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Verkaik-Kloosterman, J., </author><author>van't Veer, P., </author><author>Ocké, M. C. </author></authors></contributors><titles><title>Reduction of salt: will iodine intake remain adequate in The Netherlands?</title><secondary-title>British Journal of Nutrition</secondary-title></titles><periodical><full-title>British Journal of Nutrition</full-title></periodical><pages>1712-1718</pages><volume>104</volume><number>11</number><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>] estimated that the median iodine intake of adult women in the Netherlands was 204 µg/day.

Korevaar et al. (2016) provided urinary iodide data for only 672 women in their studies. The mean reported urinary/creatinine ratio in this subsample was 227 µg/g. Iodine intake was not assessed in Endendijk et al. (2017), although they did cite Wiersinga et al. (2001, as cited in Endendijk et al., 2017) as a study demonstrating that the study area in which the Endendijk analysis was conducted is iodine sufficient. In this study school children's median iodine levels were 154.4 µg/L (reported as 15.44 µg/dL). Estimated daily urinary output or iodine intake were not provided in this study.

Iodine intake levels appear to be similar or lower in the United States. In a recent analysis of NHANES data, Caldwell et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Caldwell</Author><Year>2013</Year><RecNum>110</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>110</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1458165747">110</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Caldwell, K.L.</author><author>Yi, P.</author><author>Mortensen, M.E.</author><author>Makhmudov, A.</author><author>Merrill, L.</author><author>Moye, J.</author></authors></contributors><titles><title>Iodine status in pregnant women in the National Children's Study and in U.S. women (15-44 Years), National Health and Nutrition Examination Study 2005-2010</title><secondary-title>Thyroid</secondary-title></titles><periodical><full-title>Thyroid</full-title></periodical><pages>927-937</pages><volume>23</volume><number>8</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>] found that the median urinary iodide excretion level in women aged 20–39 was 113 µg/g creatinine, which is much lower than that seen in Korevaar et al. (2016)'s sample. Murray et al. [ADDIN EN.CITE ADDIN EN.CITE.DATA] estimated the

lower- and upper-bound mean iodine intakes for U.S. women aged 25–45 as approximately 145 to 197 μg/day, which is in line but slightly higher than the studies of Dutch women by Brussaard et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Brussaard</Author><Year>1997</Year><RecNum>55</RecNum><DisplayText>(1997)</DisplayText><record><rec-number>55</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437143470">55</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Brussaard, J H</author><author>Hulshof, K F</author><author>Kistemaker, C</author><author>Lowik, M R</author></authors></contributors><titles><title>Adequcy of the iodine supply in the Netherlands</title><secondary-title>European Journal of Clinical Nutrition</secondary-title></titles><periodical><full-title>European Journal of Clinical Nutrition</full-title></periodical><pages>5</pages><volume>51</volume><section>11</section><dates><year>1997</year></dates><urls></urls></record></Cite></EndNote>] and lower than Verkaik-Kloosterman et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Verkaik-Kloosterman</Author><Year>2010</Year><RecNum>299</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>299</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1470950359">299</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Verkaik-Kloosterman, J., </author><author>van't Veer, P., </author><author>Ocké, M. C. </author></authors></contributors><titles><title>Reduction of salt: will iodine intake remain adequate in The Netherlands?</title><secondary-title>British Journal of Nutrition</secondary-title></titles><periodical><full-title>British Journal of Nutrition</full-title></periodical><pages>1712-1718</pages><volume>104</volume><number>11</number><dates><year>2010</year></dates><urls></urls></record></Cite></EndNote>]. Thus, there is little reason to believe that the uncertainty in iodine intake levels would have a large impact on the resulting derivation of an MCLG.

The influence of nationality on endpoints and examinations used to evaluate them may produce uncertainty when comparing study populations. For example, in Pop et al. (1999, 2003) and other Dutch studies, the Dutch version of the BSID was used to evaluate neurodevelopmental endpoints. The Dutch version of the BSID is a translation of the U.S. version and uses the same cut points for impairment [ADDIN EN.CITE <EndNote><Cite><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(Pop et al., 2003; van der Meulen & Smrkovsky, 1984)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite><Cite><Author>van der Meulen</Author><Year>1984</Year><RecNum>233</RecNum><record><rec-number>233</rec-

number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468266018">233</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>van der Meulen, B.F. </author><author>Smrkovsky, M.</author></authors></contributors><titles><title>Bayley Ontwikkelingsschalen</title></titles><dates><year>1984</year></dates><pub-location>Groningen, The Netherlands</pub-location><publisher>Kinderstudies</publisher><urls></urls></record></Cite></EndNote>]. However, Dutch norms may differ from U.S. norms, and one study found that "for all subtests… these differences are clinically relevant" [ADDIN EN.CITE <EndNote><Cite><Author>Steenis</Author><Year>2015</Year><RecNum>1911</RecNum><DisplayText>(Steenis, Verhoeven, Hessen, & van Baar, 2015)</DisplayText><record><rec-number>1911</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1503343665">1911</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Steenis, L.J.P.</author><author>Verhoeven, M.</author><author>Hessen, D.J.</author><author>van Baar, A.L.</author></authors></contributors><titles><title>Performance of Dutch children on the Bayley III: A comparison study of U.S. and Dutch norms</title><secondary-title>PLoS ONE</secondary-title></titles><periodical><full-title>PLoS ONE</full-title></periodical><volume>10</volume><number>8</number><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>].

6.5.2 Endpoint Evaluated

There are numerous indices by which to assess neurodevelopmental impacts. Some evaluate a single attribute of neurodevelopment (e.g., language delay), whereas others evaluate a broader set of attributes. The majority of neurodevelopmental indicators tests used in the cognitive studies measure indices of global neuropsychological performance. Only one study evaluated further for dose-response was based on a behavioral endpoint (Endendijk et al., 2017). Animal data show that thyroid hormone decrement affects different brain areas depending on the stage of gestation when hormone deficiency is present [ADDIN EN.CITE <EndNote><Cite><Author>Morreale de Escobar</Author><Year>2004</Year><RecNum>49</RecNum><DisplayText>(G Morreale de Escobar et al., 2004)</DisplayText><record><rec-number>49</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1437077734">49</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Morreale de Escobar, G</author><author>Obregón, M J</author><author>Escobar del Rey, F</author></authors></contributors><titles><title>Role of thyroid hormone during early brain development</title><secondary-title>European Journal of Endocrinology</secondary-title></titles><periodical><full-title>European Journal of Endocrinology</full-title></periodical><pages>U25-U37</pages><volume>151</volume><number>Suppl 3</number><dates><year>2004</year><pub-dates><date>November 1, 2004</date></pub-dates></dates><urls><related-urls><url>http://www.eje-online.org/content/151/Suppl_3/U25.abstract</url></related-urls></urls><electronic-resource-num>10.1530/eje.0.151U025</electronic-resource-num></record></Cite></EndNote>]. As such, global markers may not evaluate the most sensitive neurodevelopmental endpoint in regard to decreased maternal thyroid hormone levels depending on the phase of gestation in which a fetus may be exposed to low maternal thyroid hormone levels. Further, mothers with pre-existing thyroid disease were excluded from certain studies used in the

analysis (e.g., Korevaar et al., 2016; Finken et al., 2013), which may have potentially reduced the relationship between fT4 and neurodevelopmental outcomes in these studies. Additionally, considering the analysis for Finken et al. (2013), it is difficult to ascertain the true implications of a change in the standard deviation of reaction time, the endpoint with which there is a significant association with maternal fT4 levels.

6.5.3 Iodine Intake Data for the Study Population

Iodine intake status may impact neurodevelopmental outcomes, and the BBDR model presents dose-response information by iodine intake level. However, none of the five studies carried forward for additional quantitative analysis provided information specifically on iodine intake levels, though Korevaar et al. (2016) provided some data on urinary iodine as discussed in Section [REF _Ref492564492 \r \h]. Therefore, uncertainty exists regarding how information culled from each study relates to a specific iodine intake rate, and the corresponding fT4 changes, as predicted by the BBDR model.

6.5.4 Size of the Study Population

A larger cohort may have more power to detect a subtle difference in an outcome compared to a smaller one. Additionally, a larger study may be more easily extrapolated compared to a smaller study. However, smaller studies have benefits as well. For example, some of the standard neurodevelopmental evaluations require one-on-one assessments, which may not be feasible in cohorts with thousands of individuals. Further, a small study that does detect an association is notable given the lack of power that is associated with a small sample size.

The analyses by Pop et al. (1999; 2003) have small ($n < 30$) populations when considering the results used for quantitative analysis. However, despite a small sample size and low statistical power, the studies found statistically significant relationships between fT4 and a measure of neurodevelopment. Additionally, the Pop et al. (1999, 2003) findings of an association between maternal hypothyroxinemic levels of fT4 and adverse neurodevelopmental outcomes are supported by many other papers (i.e., the majority of Group 1 and Group 2 papers). There were 442 women in the final sample in Endendijk et al. (2017). Finken et al. (2013) and Korevaar et al. (2016) both used larger cohorts ($n > 1,700$ for both) in the analyses the EPA used to evaluate incremental changes in neurodevelopment.

6.5.5 The Method and Timing of Maternal fT4 Measurement During Pregnancy

Repeated thyroid hormone measurements give a more complete picture as to how alterations in thyroid homeostasis impact neurodevelopment throughout gestation. Given that perchlorate exposure likely does not occur in just one phase of gestation or early infancy, having a more comprehensive evaluation of the impact of thyroid hormone levels on neurodevelopment may provide a better concept of how suppressed thyroid hormone levels impact neurodevelopment throughout pregnancy or early infancy. However, this must be considered alongside the fact that the BBDR model is focused on early pregnancy. Subsequently, studies with a more complete analysis of fT4 across the course of pregnancy may be informative but it may not be possible to connect them to the output of the BBDR model. In regard to maternal thyroid hormone levels, fT4 in early pregnancy (i.e., prior to fetal thyroid hormone development, which occurs between GW 12 and GW 16) is believed to be most important in regard to neurodevelopmental outcomes (Morreale de Escobar, 2001; Morreale de Escobar et al., 2004).

All studies identified for further quantitative analysis on the relationship between maternal fT4 and neurological effects in the offspring evaluated this relationship based on a one-time fT4 measurement during pregnancy with the exception of Endendijk et al. (2017). Endendijk et al. (2017) conducted growth mixture modeling, from which the authors determined that the trajectory of maternal thyroid hormones throughout the course of pregnancy was a better predictor of internalizing problems compared to just first-trimester fT4. However, given that the BBDR model concentrates on early pregnancy, results from the analysis on the trajectories of thyroid hormones could not be used in the further dose-response analysis to inform the MCLG for perchlorate.

From evaluating the results of the literature review it appears the relationship between maternal fT4 and fetal brain development has a temporal factor, with this influence likely being greatest in early pregnancy (i.e., prior to mid-gestation). While maternal hypothyroxinemia later in pregnancy appears to be less influential, it is not without effect. For example, Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] found a dependent relationship between neurological deficits in children associated with decreases in the mother's first-trimester fT4 (at 12 GW). However, when they followed women to GW 32 they found that those women whose fT4 reverted to the normal range did not have children with MDI/PDI deficits. This rebound of fT4 occurred in at least 15 of the 57 cases that were part of the cohort that informed the function derived from Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>]. Additionally, the authors found that individuals born to mothers with consistently low fT4 had the worst neurodevelopmental outcomes. Further, Endendijk et al. (2017) found that individuals in a group with the highest and non-increasing TSH levels with the lowest fT4 that decreased the least amount throughout the course of pregnancy showed more anxiety/depression symptoms compared to groups with either increasing TSH and decreasing fT4 at

intermediate levels or lowest and increasing TSH with highest and decreasing fT4 levels. Subsequently, how maternal thyroid hormones change throughout the course of pregnancy represents an uncontrolled source of variability given that what happens after GW 12 to maternal fT4 levels appears to have an impact on neurodevelopmental outcome.

If low fT4 later in pregnancy also causes further damage beyond the effects in the first trimester, it is likely that a steeper dose-response slope would have been found if only those women who were consistently hypothyroxinemic throughout pregnancy were evaluated (see Pop et al., 2003, Figure 3). This weakening of the correlation between hormone and outcome is likely to lessen the perchlorate dose-response slope on neurodevelopment because it relies on both the relationship between perchlorate's effect on hormones (BBDR model) and then hormones' effect on outcome.

Also related to the method of assessing fT4 is that uncertainties exist in regard to the analytical approach to evaluating fT4 levels. Although a working group was put together by the International Federation of Clinical Chemistry and Laboratory Medicine in 2005 to standardize thyroid function tests primarily for TSH and fT4, this standardization has not yet been achieved [ADDIN EN.CITE <EndNote><Cite><Author>Thienpont</Author><Year>2015</Year><RecNum>276</RecNum><DisplayText>(Thienpont, Faix, & Beastall, 2015)</DisplayText><record><rec-number>276</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468523238">276</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Thienpont, L. M.</author><author>Faix, J. D.</author><author>Beastall, G.</author></authors></contributors><auth-address>Mass Spectrometry Reference Laboratory LAC at Ghent University, Ghent, Belgium.</auth-address><titles><title>Standardization of FT4 and harmonization of TSH measurements - a request for input from endocrinologists and other physicians</title><secondary-title>Endocrine Journal</secondary-title></titles><periodical><full-title>Endocrine Journal</full-title></periodical><pages>855-6</pages><volume>62</volume><number>10</number><edition>2015/07/28</edition><dates><year>2015</year></dates><isbn>1348-4540 (Electronic)
0918-8959 (Linking)</isbn><accession-num>26211473</accession-num><urls></urls><electronic-resource-num>10.1507/endocrj.EJ15-0382</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. As such, assay results obtained at different times or in different countries may not be directly comparable due to differences in analytical procedures. fT4 could be as little as 1% of the circulating total T4 concentration [ADDIN EN.CITE <EndNote><Cite><Author>Koulouri</Author><Year>2013</Year><RecNum>275</RecNum><DisplayText>(Koulouri, Moran, Halsall, Chatterjee, & Gurnell, 2013)</DisplayText><record><rec-number>275</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468523217">275</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Koulouri, O.</author><author>Moran, C.</author><author>Halsall, D.</author><author>Chatterjee, K.</author><author>Gurnell, M.</author></authors></contributors><auth-address>Metabolic Research Laboratories, Wellcome Trust - MRC Institute of Metabolic Science, University of Cambridge and National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.</auth-address><titles><title>Pitfalls in the measurement and interpretation of thyroid function tests</title><secondary-title>Best Practice

& Research Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>Best Practice & Research Clinical Endocrinology & Metabolism</full-title></periodical><pages>745-62</pages><volume>27</volume><number>6</number><edition>2013/11/28</edition><keywords><keyword>Female</keyword><keyword>Humans</keyword><keyword>Hyperthyroidism/blood/diagnosis/physiopathology</keyword><keyword>Hypothyroidism/blood/diagnosis/physiopathology</keyword><keyword>Male</keyword><keyword>Pregnancy</keyword><keyword>Thyroid Function Tests</keyword><keyword>Thyroid Gland/physiopathology</keyword><keyword>Thyroid Hormones/analysis</keyword></keywords><dates><year>2013</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>1878-1594 (Electronic)
1521-690X (Linking)</isbn><accession-num>24275187</accession-num><urls></urls><custom2>3857600</custom2><electronic-resource-num>10.1016/j.beem.2013.10.003</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>], making it difficult to measure. The bulk of the enzyme-linked immunosorbent assays used for measurement of fT4 require no pre-treatment or serum extraction procedures to be undertaken. Rather, they rely on competitive binding assays that could be affected by changes in endogenous serum protein ratios, displacing agents such as heparin, and the presence of other antibodies that may block the action of the assay antibody [ADDIN EN.CITE <EndNote><Cite><Author>Koulouri</Author><Year>2013</Year><RecNum>275</RecNum><DisplayText>(Koulouri et al., 2013)</DisplayText><record><rec-number>275</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468523217">275</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Koulouri, O.</author><author>Moran, C.</author><author>Halsall, D.</author><author>Chatterjee, K.</author><author>Gurnell, M.</author></authors></contributors><auth-address>Metabolic Research Laboratories, Wellcome Trust - MRC Institute of Metabolic Science, University of Cambridge and National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.</auth-address><titles><title>Pitfalls in the measurement and interpretation of thyroid function tests</title><secondary-title>Best Practice & Research Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>Best Practice & Research Clinical Endocrinology & Metabolism</full-title></periodical><pages>745-62</pages><volume>27</volume><number>6</number><edition>2013/11/28</edition><keywords><keyword>Female</keyword><keyword>Humans</keyword><keyword>Hyperthyroidism/blood/diagnosis/physiopathology</keyword><keyword>Hypothyroidism/blood/diagnosis/physiopathology</keyword><keyword>Male</keyword><keyword>Pregnancy</keyword><keyword>Thyroid Function Tests</keyword><keyword>Thyroid Gland/physiopathology</keyword><keyword>Thyroid Hormones/analysis</keyword></keywords><dates><year>2013</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>1878-1594 (Electronic)
1521-690X (Linking)</isbn><accession-num>24275187</accession-num><urls></urls><custom2>3857600</custom2><electronic-resource-num>10.1016/j.beem.2013.10.003</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. Correlation between liquid chromatographic tandem mass spectrometry (MS) values versus standard immunoassay techniques

showed that there was a correlation coefficient of approximately 0.75 for fT4, unlike total T4, which had a correlation coefficient of 0.91–0.95. This was likely due to the ability of tandem MS to better measure fT4 compared to immunoassay [ADDIN EN.CITE ADDIN EN.CITE.DATA].

In regards to the studies further evaluated for quantitative assessment, both Pop et al. studies used immunoassay techniques to assess the fT4 levels in their cohort. Korevaar et al. (2016) and Finken et al. (2013) used chemiluminescence assays, as did Endendijk et al. (2017). Additionally, there could be individual variation in fT4 measurements or interference from some over-the-counter medications, such as aspirin and other NSAIDs, which could displace thyroid hormones on TBG or TTR, causing artificial elevations in fT4 measurement [ADDIN EN.CITE <EndNote><Cite><Author>Koulouri</Author><Year>2013</Year><RecNum>275</RecNum><DisplayText>(Koulouri et al., 2013)</DisplayText><record><rec-number>275</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1468523217">275</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Koulouri, O.</author><author>Moran, C.</author><author>Halsall, D.</author><author>Chatterjee, K.</author><author>Gurnell, M.</author></authors></contributors><auth-address>Metabolic Research Laboratories, Wellcome Trust - MRC Institute of Metabolic Science, University of Cambridge and National Institute for Health Research Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.</auth-address><titles><title>Pitfalls in the measurement and interpretation of thyroid function tests</title><secondary-title>Best Practice & Research Clinical Endocrinology & Metabolism</secondary-title></titles><periodical><full-title>Best Practice & Research Clinical Endocrinology & Metabolism</full-title></periodical><pages>745-62</pages><volume>27</volume><number>6</number><edition>2013/11/28</edition><keywords><keyword>Female</keyword><keyword>Humans</keyword><keyword>Hyperthyroidism/blood/diagnosis/physiopathology</keyword><keyword>Hypothyroidism/blood/diagnosis/physiopathology</keyword><keyword>Male</keyword><keyword>Pregnancy</keyword><keyword>Thyroid Function Tests</keyword><keyword>Thyroid Gland/physiopathology</keyword><keyword>Thyroid Hormones/analysis</keyword></keywords><dates><year>2013</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>1878-1594 (Electronic)
1521-690X (Linking)</isbn><accession-num>24275187</accession-num><urls></urls><custom2>3857600</custom2><electronic-resource-num>10.1016/j.beem.2013.10.003</electronic-resource-num><remote-database-provider>NLM</remote-database-provider><language>eng</language></record></Cite></EndNote>]. Thus, the true fT4 levels of the subjects in the papers used for further analysis may differ from the values obtained in their analyses. However, because all individuals in the papers were assessed using the same techniques, any bias resulting from this source of uncertainty would likely be random and would tend to bias toward the null.

6.5.6 Uncertainties Related to the Quantitative Analyses

There is uncertainty regarding the true fT4 levels at various percentiles in the distribution around the median output from the BBDR model. In most analyses presented in this report, unit changes in endpoints due to changes in fT4 assuming a particular dose of perchlorate are the same across fT4 percentiles. This is due to the linear relationships assumed between fT4 and each endpoint modeled in the epidemiologic studies, along with the EPA's assumption of normality of errors around the predicted median fT4 values output by the BBDR model. The exceptions to this pattern of results are

the analysis results based on the Korevaar et al. (2016) data (both the original quadratic function and the EPA reanalysis). In these analyses, larger unit changes are seen with decreasing percentiles of fT4, which is due to the assumption of non-linear relationships between fT4 and IQ, and especially due to the log-transformation of fT4 in the models. This pattern of results agrees with the hypothesis that decreases in fT4 from lower base levels of fT4 have a larger effect on neurodevelopmental endpoints than at higher base levels of fT4.

One uncertainty consideration, specifically when evaluating the lower percentiles of fT4 from the derived distributions, is the potential for extrapolating beyond the data from which the function was derived. For example, [REF _Ref492567077 \h] summarizes the lowest fT4 value observed in each of the studies that the EPA evaluated further. Given that a lower fT4 level is associated with worse neurodevelopmental outcomes, there is no reason to believe that predictions of fT4's effect on neurodevelopment are being overestimated by falling below the observed range.

Table [SEQ Table * ARABIC]. Lowest Observed fT4 Levels in Group 1 Studies Used for Analysis

Study	Lowest Observed fT4 (pmol/L)
Finken et al. (2013)[a]	< 6.5
Korevaar et al. (2016)	6.38
Pop et al. (1999)[b]	7.86
Pop et al. (2003)[b]	8.39
Endendijk et al. (2017)[c]	< 11.97

[a] Full range not presented. 6.5 pmol/L represents the 2.5th percentile fT4.
[b] Range of data estimated from digitized dataset.
[c] Full range not presented. 11.97 pmol/L represents the 2.5th percentile fT4.

Further, several of the dose-response functions presented in this report linking maternal fT4 to an offspring's neurodevelopment are based on the EPA's own digitization of data from a figure depicting a correlation or regression analysis (Pop et al., 1999, 2003). The EPA has not used multiple regression analysis to adjust for confounding or interacting variables because it does not have the raw data to do so. However, as discussed in Section [REF _Ref482192481 \r \h], Pop et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Pop</Author><Year>2003</Year><RecNum>25</RecNum><DisplayText>(2003)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047641">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Pop, V J</author><author>Brouwers, E P</author><author>Vader, H L</author><author>Vulsma, T</author><author>van Baar, A L</author><author>de Vijlder, J J</author></authors></contributors><titles><title>Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study</title><secondary-title>Clinical Endocrinology</secondary-title></titles><periodical><full-title>Clinical Endocrinology</full-title></periodical><pages>282-288</pages><volume>59</volume><section>282</section><dates><year>2003</year></dates><urls></urls></record></Cite></EndNote>] took steps to mitigate the potential for residual confounding

during the development of the cohorts for which they conducted their evaluation. Specifically, women were excluded from analysis due to pregnancy and child outcome-related factors that could interfere with a child's neurodevelopmental outcome. For example, women were excluded if they had at least one episode of reported post-partum depression. Additionally, as outlined in the Pop et al. (1999) summary, in their logistic regression analysis they found a much higher relative risk after controlling for confounding variables (RR = 5.8; 95% CI: 1.3-12.6) compared to their univariate analysis (RR = 3.6; 95% CI: 1.1-12.1). This implies that the current effect estimates derived from the Pop et al. studies may be underestimating the true effect of fT4 level in the maternal hypothyroxinemic range and its impact on neurodevelopment. The analyses provided by Korevaar et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Korevaar</Author><Year>2016</Year><RecNum>313</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>313</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832236">313</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, Tim I. M.</author><author>Muetzel, Ryan</author><author>Medici, Marco</author><author>Chaker, Layal</author><author>Jaddoe, Vincent W. V.</author><author>de Rijke, Yolanda B.</author><author>Steegers, Eric A. P.</author><author>Visser, Theo J.</author><author>White, Tonya</author><author>Tiemeier, Henning</author><author>Peeters, Robin P.</author></authors></contributors><titles><title>Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study</title><secondary-title>The Lancet Diabetes & Endocrinology</secondary-title></titles><periodical><full-title>The Lancet Diabetes & Endocrinology</full-title></periodical><pages>35-43</pages><volume>4</volume><number>1</number><dates><year>2016</year></dates><isbn>22138587</isbn><urls></urls><electronic-resource-num>10.1016/s2213-8587(15)00327-7</electronic-resource-num></record></Cite></EndNote>] and Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>] did control for confounding variables, and beta estimates were either provided in the primary studies or calculated by the EPA with the underlying dataset. The EPA reanalysis of the Korevaar et al. (2016) study data controls for a more appropriate set of confounders, while also estimating a spline function that more closely fits the underlying data than the original Korevaar et al. (2016) analysis function, specifically for the lower end of the fT4 spectrum.

Additionally, some studies that were not used for further quantitative analysis found associations that were attenuated when adjusting models for potential confounders (e.g., Gyllenberg et al., 2016; Modesto et al., 2015) given the impact that variables such as smoking may have on both thyroid hormone levels and neurodevelopmental outcomes. For example, Gyllenberg et al. (2016) observed an association between fT4 and risk of schizophrenia in their unadjusted analysis, but after individually adjusting for maternal smoking during early gestation and collectively adjusting for maternal psychiatric history, province of birth, and maternal smoking, the association between maternal hypothyroxinemia and offspring schizophrenia was no longer significant. The adjustment for maternal smoking resulted in a greater than 20% change in the odds ratio. According to the authors, the finding that the continuous measure of fT4 lost statistical significance while there was still an association between maternal hypothyroxinemia after adjusting for confounders "suggests that the relationship between maternal fT4 and schizophrenia is present only when fT4 levels are below a particular threshold" (Gyllenberg et al., 2016, p. 966). Other factors that were not measured or controlled by the papers assessed, such as maternal lead or arsenic levels, are additional sources of uncontrolled variability that would tend to weaken the correlation between fT4 and neurodevelopment and thus perchlorate and neurodevelopment.

7. Informing the Derivation of an MCLG: Hypothyroxinemia

The previous section outlined a process by which the output of the BBDR model was connected to neurodevelopmental outcomes in the offspring of pregnant women who are exposed to perchlorate in pregnancy. This connection was made by using epidemiologic literature to connect shifts in fT4, as predicted by the BBDR model, to various indicators of neurodevelopment.

An alternative option to inform future decisions on the derivation of an MCLG using the BBDR model is to evaluate a shift in the proportion of the population that will fall below a hypothyroxinemic cut point, given exposure to perchlorate. This approach does not directly connect the BBDR output to neurodevelopment. However, for pregnant mothers in early pregnancy, this shift could be related to avoiding an increase in the offspring population's risk of adverse neurodevelopmental impacts given the preponderance of evidence located in the EPA's literature review that finds an association between hypothyroxinemia and adverse neurodevelopmental outcomes, as outlined in Section [REF _Ref482392166 \r \h].

For example, many Group 2 studies found an increased risk of adverse neurodevelopmental outcomes in the offspring of mothers with maternal hypothyroxinemia, compared to non-hypothyroxinemic mothers. These effects included decreased performance on the Bayley Scales for Infant Development (Costeira et al., 2011; Júlvez et al., 2013; Li et al., 2010), behavioral assessment scales (Kooistra et al., 2006), and increased fetal and infant head size (van Mil et al., 2012). Additionally, Päkkilä et al. (2015) found increased odds of having repeated a school class as assessed in 16-year-olds. Further, two meta-analyses (Fan and Wu, 2016; Wang et al., 2016) concluded that low fT4 is associated with adverse neurodevelopmental outcomes including increased risk of delayed cognitive development and lower intelligence and motor scores. Thompson et al. (2018) found that compared to those children born to euthyroid mothers, children born to hypothyroxinemic mothers were significantly more likely to show signs of intellectual impairment.

In addition to presenting regression analyses that evaluated how thyroid hormone levels impact neurodevelopment, 11 Group 1 studies also found strong associations between maternal hypothyroxinemia and neurodevelopment outcomes in offspring when compared to non-hypothyroxinemic groups. That is, of the 13 studies in Group 1 that performed a categorical analysis, the only studies that did not find an adverse association between maternal hypothyroxinemia and a measure of neurodevelopment were Oken et al. (2009) and Kasatkina et al. (2006). As previously discussed, Oken et al. (2009) evaluated only T4, not fT4, which may be an explanation for the null finding. The findings from Kasatkina et al. (2006) were not assessed further, as the study was designated as Tier 3 (high ROB).

In evaluating neurodevelopment with the BSID, both Pop et al. studies (1999, 2003) found the relationship between reduced fT4 and reduced MDI or PDI only in hypothyroxinemic first-trimester pregnant mothers. Further, both Ghassabian et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Ghassabian</Author><Year>2014</Year><RecNum>10</RecNum><DisplayText>(2014)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047632">10</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Ghassabian, A</author><author>Marroun, H E</author><author>Peeters, R P</author><author>Jaddoe, V W</author><author>Hofman, A</author><author>Verhulst, F C</author><author>Tiemeier, H</author><author>White,

T</author></authors></contributors><titles><title>Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>2383-2390</pages><volume>99</volume><number>7</number><section>2383</section><dates><year>2014</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2013-4281</electronic-resource-num></record></Cite></EndNote>] and Korevaar et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Korevaar</Author><Year>2016</Year><RecNum>313</RecNum><DisplayText>(2016)</DisplayText><record><rec-number>313</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1491832236">313</key><key app="ENWeb" db-id="">0</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Korevaar, Tim I. M.</author><author>Muetzel, Ryan</author><author>Medici, Marco</author><author>Chaker, Layal</author><author>Jaddoe, Vincent W. V.</author><author>de Rijke, Yolanda B.</author><author>Steegers, Eric A. P.</author><author>Visser, Theo J.</author><author>White, Tonya</author><author>Tiemeier, Henning</author><author>Peeters, Robin P.</author></authors></contributors><titles><title>Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study</title><secondary-title>The Lancet Diabetes & Endocrinology</secondary-title></titles><periodical><full-title>The Lancet Diabetes & Endocrinology</full-title></periodical><pages>35-43</pages><volume>4</volume><number>1</number><dates><year>2016</year></dates><isbn>22138587</isbn><urls></urls><electronic-resource-num>10.1016/s2213-8587(15)00327-7</electronic-resource-num></record></Cite></EndNote>] found maternal hypothyroxinemia to be associated with lower non-verbal intelligence scores in offspring compared to IQ scores from offspring of non-hypothyroxinemic mothers. Finken et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Finken</Author><Year>2013</Year><RecNum>9</RecNum><DisplayText>(2013)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29" timestamp="1432047631">9</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Finken, M J J</author><author>van Eijsden, M</author><author>Loomans, E M</author><author>Vrijkotte, T G M</author><author>Rotteveel, J</author></authors></contributors><titles><title>Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring</title><secondary-title>Journal of Clinical Endocrinology and Metabolism</secondary-title></titles><periodical><full-title>Journal of Clinical Endocrinology and Metabolism</full-title></periodical><pages>1417-1426</pages><volume>98</volume><number>4</number><section>1417</section><dates><year>2013</year></dates><urls></urls><electronic-resource-num>10.1210/jc.2012-3389</electronic-resource-num></record></Cite></EndNote>] found increased baseline reaction time and standard deviation of reaction time in offspring of hypothyroxinemic mothers compared to non-hypothyroxinemic mothers. Henrichs et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Henrichs</Author><Year>2010</Year><RecNum>16</RecNum><DisplayText>(2010)</DisplayText><record><rec-number>16</rec-number><foreign-keys><key app="EN" db-id="z9t0avxvzdfermedxe5vxfpkax2vzp0ftv29"